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CONTENTS FOR DECEMBER, 1936

Original Communications

Department of Clinical Reports

Department of Reviews and Abstracts

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Original Communications

THE COMMONEST CAUSE OF HYPERTROPHY OF THE RIGHT VENTRICLE—LEFT VENTRICULAR STRAIN AND FAILURE*

WILLIAM PAUL THOMPSON,† M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

IN 1933 White and McGinn[1] emphasized the importance of the recognition of the clinical aspects of left ventricular strain and failure without failure of the right ventricle of the heart. They pointed out "the astonishing fact that so little attention has been paid by the English-speaking world . . . . to this state of congestive failure of the left ventricle without congestive failure of the right ventricle." As a logical corollary to this conception, we have become interested in the effect that pure left ventricular strain, due to chronic arterial hypertension, aortic valvular disease, and infarcts of the left ventricle, may have in producing hypertrophy of the right ventricle which is not subjected to the primary strain.

It is known that general enlargement of the heart may occur in pure left-sided strain, for at autopsy there is often an appreciable enlargement of the right ventricle, as well as of the left, in patients whose hearts were presumably subjected only to left ventricular strain. The sequence of events which produces this right-sided enlargement has been clearly summarized by Wiggers,[2] who pointed out that, when the left ventricle begins to weaken and fail, it "dilates enormously," and that "this marks the onset of cardiac fatigue. Straub's experiments indicate that when this occurs the pressures in the left auricle become greatly elevated and the lungs markedly distended." It should be added that dilatation of the left ventricle may be associated with the production of a relative mitral valve regurgitation, merely through stretching of the mitral ring. Wiggers further states that

*From the Cardiac Laboratory and Clinics of the Massachusetts General Hospital. Read in Abstract at the Annual Meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1936.

†Dalton Scholar, Massachusetts General Hospital, 1935-36.

"the right ventricle, in consequence, is compelled to contract against a greater load; it then passes through the same phases of cardiac strain as the left." We have, then, an adequate explanation for right ventricular enlargement when the left ventricle has been the primary seat of the strain. According to Wiggers, "the enlargement may affect the entire heart, but naturally occurs predominantly in the ventricle which is called upon to bear the brunt of the excess work." There is no doubt that this statement is true, but two cases* have recently come to our attention in which the predominant hypertrophy was on the right side, while the left side had been the primary seat of the strain. We shall review them briefly.

The first case was a man, aged forty-three years, with aortic stenosis and insufficiency without other valvular disease, who had had marked congestive failure of both ventricles for eighteen months. The electrocardiogram revealed *right* axis deviation of marked degree. At post-mortem examination there was actually preponderant hypertrophy of the right ventricle, its wall measuring 8 mm. in thickness (normal 3), while the left measured 17 (normal 10). The heart was markedly enlarged, its weight being 910 gm. No factor producing primary right ventricular strain was found.

The second case was similar. The patient was a man, aged thirty-eight years, who had had severe congestive failure of both ventricles for three months. He also had aortic stenosis and insufficiency, and his electrocardiogram revealed a moderate degree of *right* axis deviation. Again the right ventricle was preponderantly hypertrophied, its wall measuring 11 mm., while the left measured 22 mm. The heart weighed 750 gm.

Obviously these two cases do not represent a usual occurrence in left ventricular strain, but they do demonstrate that the side of the heart which is free from the primary strain may be not only considerably hypertrophied, but that its hypertrophy may actually be preponderant.

The present study is concerned with the causes of hypertrophy of the right ventricle and the importance of pure left ventricular strain in producing this hypertrophy. Our procedure has been to study cases in which right ventricular hypertrophy had been demonstrated at post-mortem examination, and to determine, from both the clinical and the post-mortem data, the seat of the strain. We are concerned, then, with right ventricular hypertrophy per se, and not with preponderant hypertrophy, since, for the moment, the degree of left ventricular hypertrophy remains out of consideration.

The protocols of 2,524 consecutive autopsies at the Massachusetts General Hospital† were reviewed, and all cases in which the right

*We are indebted to Dr. S. B. Wolbach, of the Department of Pathology at the Peter Bent Brigham Hospital, for permission to cite these cases.

†Our thanks are due to Dr. Tracy B. Mallory, chief of the Department of Pathology for allowing us to use his files and records.

ventricular wall measured 5 mm.* or more in thickness were selected for study. Partial examinations which did not include the heart and examinations of infants and children were excluded (a total of 524 cases), so that 2,000 adult hearts remained for review. Among these 2,000 cases there were 704 with hypertrophy of the right ventricle. These 704 cases were then divided into four groups: first, those in which there had been primary right ventricular strain; second, those with primary left ventricular strain; third, those with primary strain on both sides of the heart; and fourth, those in which we could find no clear factor of strain on either side of the heart. The factors that we have considered responsible for these various kinds of strain are shown in Table I.

TABLE I

FACTORS PRODUCING STRAIN ON THE HEART

PRIMARY LEFT VENTRICULAR STRAIN	PRIMARY RIGHT VENTRICULAR STRAIN	PRIMARY STRAIN ON BOTH VENTRICLES
Arterial hypertension	Mitral stenosis	Mitral insufficiency
Aortic stenosis	Pulmonic valve stenosis	Multiple valvular disease (chiefly aortic and mitral)
Aortic insufficiency	Pulmonic valve insufficiency	Severe anemia
Infarction of the left ventricle	Pulmonary endarteritis	Arterial hypertension, aortic valve disease, or myocardial infarction *plus* factors producing right ventricular strain
	Organic tricuspid insufficiency	
	Marked pulmonary fibrosis	
	Marked pulmonary emphysema	
PRIMARY STRAIN ON LEFT VENTRICLE AND SECONDARY STRAIN ON RIGHT VENTRICLE		
Factors listed in the first column above plus failure of the left ventricle		

Table II shows the number of cases in each of these groups, each group being divided according to the degree of right ventricular hypertrophy as shown by the thickness of the wall.

In about one-fourth of the cases, those in the last column, we could find no factor of strain which allowed us to place them in one of the other groups. Many of these hearts had coronary artery disease without occlusion or myocardial infarction, cases which perhaps might fairly have been classed as having left ventricular strain (since the coronary supply to the left ventricle is ordinarily more extensively involved in a sclerotic process than is that to the right), but without infarction of the left ventricle we have not felt ourselves justified in so grouping them. Without doubt, some of the patients whose hearts we have listed as having been under no strain did have arterial hypertension, their blood pressures being normal or low while they were in

*This thickness was chosen on the basis that the normal right ventricle measures 3 and sometimes 4 mm. in thickness.

The thickness of the right ventricular wall is routinely measured at a point on the anterior surface midway between the apex and the base of the ventricle.

TABLE II

CLASSIFICATION OF CASES IN WHICH THE RIGHT VENTRICULAR WALL MEASURED 5 MM. OR MORE IN THICKNESS

RIGHT VENTRICULAR WALL	TOTAL NUMBER OF CASES	PURE RIGHT VENTRICULAR STRAIN	STRAIN ON BOTH VENTRICLES	PURE LEFT VENTRICULAR STRAIN	NO CLEAR STRAIN ON EITHER VENTRICLE
5 mm.	345	25	57	154	109
6 mm.	203	12	37	108	46
7 mm.	77	7	21	36	13
8 mm.	42	6	16	16	4
9 mm.	12	2	1	8	1
10 mm.	8	2	5	1	0
11 mm.	8	6	0	2	0
12 mm.	5	2	2	1	0
13 mm.	1	0	1	0	0
14 mm.	2	1	1	0	0
16 mm.	1	1	0	0	0
Total	704	64	141	326	173

the moribund state presented during their stay in the hospital. Again, unquestionably there are a number of normal hearts in this column, hearts with a normal weight from patients without clinical or pathological evidence of heart disease. This latter group leads us to believe that in a few instances the normal right ventricle may measure as much as 5 mm. in thickness.

For purposes of comparison we have combined the cases with pure right ventricular strain with those in which there was strain on both sides of the heart, so that all cases with any element of primary right-sided strain may be compared with those in which there was pure left-sided strain. This comparison is shown in Table III. In about 61 per cent of the cases with right ventricular hypertrophy, the cause

TABLE III

ALL CASES WITH STRAIN. CASES WITH PRIMARY RIGHT VENTRICULAR STRAIN AND THOSE WITH PRIMARY STRAIN ON BOTH VENTRICLES HAVE BEEN COMBINED FOR COMPARISON WITH THOSE HAVING PURE LEFT VENTRICULAR STRAIN

RIGHT VENTRICULAR WALL	TOTAL WITH RIGHT VENTRICULAR STRAIN	PURE LEFT VENTRICULAR STRAIN
5 mm.	82	154
6 mm.	49	108
7 mm.	28	36
8 mm.	22	16
9 mm.	3	8
10 mm.	7	1
11 mm.	6	2
12 mm.	4	1
13 mm.	1	0
14 mm.	2	0
16 mm.	1	0
Total	205	326

is seen to be strain on the left ventricle. This figure would very likely be even greater if we had considered coronary artery disease without myocardial infarction as a cause of left ventricular strain, and if the antecedent blood pressures in the moribund patients were known.

Inspection of Table III shows that when a high degree of hypertrophy of the right ventricle is found, there has probably been some factor producing primary right ventricular strain. In Table IV we have added together all cases in which the right ventricular wall measured 5 mm. *or more*, 6 mm. *or more*, and so on. It is apparent that even when the measurement is 6 mm. or more, left ventricular strain is still the more important cause. When measurements of 7 mm. or more are considered, there are approximately equal numbers of cases in both groups. It is only when marked hypertrophy with measurements of 8 or 9 mm. or more is considered that primary right ventricular strain becomes appreciably more frequent as the cause. It is notable, however, that measurements as great as 12 mm. for the right ventricle were found when the strain had been at first purely left-sided.

TABLE IV

IMPORTANCE OF PURE LEFT VENTRICULAR STRAIN IN PRODUCING THE VARIOUS DEGREES OF RIGHT VENTRICULAR HYPERTROPHY

ALL CASES WITH THE RIGHT WALL MEASURING	NUMBER OF CASES	
	RIGHT VENTRICULAR STRAIN	PURE LEFT VENTRICULAR STRAIN
5 mm. or more	205	326
6 mm. or more	123	172
7 mm. or more	74	64
8 mm. or more	46	28
9 mm. or more	24	12
10 mm. or more	21	4
11 mm. or more	14	3
12 mm. or more	8	1
13 mm. or more	4	0

Effect of Failure of the Left Ventricle Upon the Degree of Right Ventricular Hypertrophy.—Presumably, when the left ventricle is under the strain of arterial hypertension, aortic valvular disease, or myocardial infarction, this strain should not produce pulmonary engorgement and secondary right ventricular strain so long as the left ventricle is able to adjust itself to this strain. We should not, then, expect to find hypertrophy of the right ventricle under such circumstances. In order to study this point, we have reviewed all cases in the files of the Massachusetts General Hospital Department of Pathology which had been diagnosed hypertensive heart disease, aortic valvular disease, and old infarction of the left ventricle. These cases were selected without regard to the presence or absence of hypertrophy of the right ventricle. The clinical records were then examined for symp-

toms and signs of heart failure. Dyspnea, even without other symptoms or signs, was considered evidence of left ventricular failure, and was usually the first to appear. The cases were then divided into two groups: first, those which had never had failure, or had had it only as a terminal event, beginning in no instance more than two weeks before death; and second, those which had had symptoms or signs of left ventricular failure for two months or more. This period of two months was arbitrarily chosen because we felt that it should be sufficient to allow hypertrophy of the right ventricle in response to a newly imposed strain. A large intermediate group was discarded. Table V shows the average thickness of the right ventricular wall in these two groups.

TABLE V

CASES WITH PURE LEFT VENTRICULAR STRAIN

	NUMBER OF CASES	AVERAGE THICKNESS OF RIGHT VENTRICULAR WALL
No clinical evidence of failure	44	4.8 mm.
Failure of left ventricle	91	5.5 mm.

Two things are evident from Table V: first, that in cases with pure left ventricular strain, the right ventricle hypertrophies regardless of the presence or absence of clinical evidence of failure of the left ventricle; and second, that the superimposition of failure adds to the degree of right ventricular hypertrophy. The explanation for this second fact is obvious and in accord with what was anticipated. Why right ventricular hypertrophy should occur in well-compensated left ventricular strain is not at first entirely clear. Very likely some of the cases we classed as showing no failure did have failure, and the facts were not accurately recorded in the case histories, but this should not be so in any appreciable number of them. More probably, there is frequently a state of slight pulmonary vascular engorgement, and consequent strain on the right ventricle, in cases with pure left-sided strain, even though dilatation of the left ventricle and mitral ring has not occurred and there is no functional mitral regurgitation. A slight increase in pulmonary arterial pressure, without more evidence than that of failure of the left ventricle, would then seem likely and is in keeping with the observed facts.

Comparison of the Degree of Right Ventricular Hypertrophy in Pure Left Ventricular Strain With That in Right-Sided Strain.—For this comparison, an additional group of cases having primary right ventricular strain was selected from the files, no attention being given to the presence or absence of right ventricular hypertrophy. These were similarly divided into two groups, those without symptoms or signs of pulmonary engorgement (such as might result from the obstruction caused by mitral stenosis), and those with such symptoms or

signs for two months or more. The averages are shown in Table VI. It is evident again that pulmonary engorgement increases the degree of hypertrophy seen in the right ventricle. It is worthy of note, however, that on the average, the right ventricle is hypertrophied almost as much in well-compensated left ventricular strain as it is when there has been primary right ventricular strain, as shown by the two average figures, 4.8 and 5.0 mm. It seems reasonable, therefore, to regard an average thickness of 4.8 mm. for the right ventricular wall as indicative of hypertrophy.

TABLE VI

	NUMBER OF CASES	AVERAGE THICKNESS OF RIGHT VENTRICULAR WALL
Without obvious failure or pulmonary engorgement		
Right ventricular strain	47	5.0 mm.
Pure left ventricular strain	44	4.8 mm.
With failure or pulmonary engorgement		
Right ventricular strain	51	6.0 mm.
Pure left ventricular strain	91	5.5 mm.

TABLE VII

PURE LEFT VENTRICULAR STRAIN: RELATIONSHIP BETWEEN THE THICKNESS OF THE RIGHT AND LEFT VENTRICULAR WALLS*

THICKNESS OF RIGHT VENTRICULAR WALL	THICKNESS OF LEFT VENTRICULAR WALL IN MILLIMETERS																						
	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	30	32
5 mm.	1	–	4	3	9	9	10	18	14	15	28	7	17	4	4	2	–	–	–	–	1	–	–
6 mm.	1	3	–	1	1	2	5	11	12	9	16	8	12	3	6	4	5	3	–	2	–	2	1
7 mm.	–	–	1	–	–	1	3	3	2	5	3	2	4	2	1	3	1	–	–	–	1	2	–
8 mm.	–	–	–	–	–	–	–	–	1	3	1	–	6	–	1	1	–	–	–	–	–	–	–
9 mm.	–	–	–	–	–	–	1	–	–	–	2	–	–	–	2	–	2	–	–	–	–	–	–
10 mm.	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–
11 mm.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	1	–	–	–	–
12 mm.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–

*Each figure indicates the number of cases with a given thickness of each of the ventricular walls; thus, there were 18 cases in which the right ventricular wall was 5 mm. and the left 15 mm. in thickness.

Preponderant Hypertrophy of the Right Ventricle in Pure Left Ventricular Strain.—Table VII shows that there were a number of cases in which the comparative measurements of the two ventricular walls suggest preponderant hypertrophy of the right ventricle when the strain had been wholly left-sided. There were, in fact, twenty cases in which the right ventricle was fully half as thick as the left ventricle. This is a striking relative increase in the thickness of the right

ventricle when one considers that the normal figures are in the neighborhood of 3 to 4 and 9 to 10 mm. for the right and left walls, respectively.

Among the ninety-four electrocardiograms without intraventricular or bundle-branch block that were available in the cases with pure left-sided strain, there were four with right axis deviation and many more that failed to show the left deviation that would be expected in such strain. In the four cases with right deviations, the measurements for the right and left ventricles were 8 and 16 mm., 6 and 19 mm., 6 and 15 mm., and 6 and 19 mm. In two of these four cases there was considerable dilatation of the right ventricle, while in two no mention was made of the size of the cavities. In these cases there was doubtless preponderant enlargement of the right ventricle, even though the measurements may not prove it. It is unfortunate that more electrocardiograms were not available, for had there been, additional instances of right axis deviation would probably have been found.

COMMENT

We are, of course, aware of the unreliability of the thickness of a ventricular wall as the sole guide to the degree of its hypertrophy. Herrmann and Wilson[3] in their dissections of fifty-nine hearts, showed great variations in the weights of the ventricles, when weighed separately, for a given thickness. It is obvious that a right ventricle measuring but 4 mm. in thickness may have a weight greatly above the normal if the cavity is markedly dilated, and that it may weigh even more than a wall measuring 6 or 7 mm. in thickness surrounding a cavity of normal size. We believe, however, that our conclusions, drawn from this large number of cases, are valid, since dilatation of the right side of the heart was so frequently found in the cases with increased thickness of the right ventricular wall.

Errors in the interpretation of the measurements may arise from failure to note the state of myocardial relaxation or contraction during post-mortem examination, although this should lead to little error when dealing with a large series, since it is uncommon to find a heart in systole at autopsy. In not more than three or four instances was such a state noted in our cases, while almost invariably the comment was made that the myocardium, particularly that of the right ventricle, was relaxed and flabby, dilatation often being marked.

We believe that it is particularly significant that this collection of cases comes from New England, where rheumatic heart involvement (usually mitral disease which causes right ventricular strain) is very common. White and Jones[4] found in 1928 that this etiology was responsible for 54 per cent of the heart disease in patients coming to the Massachusetts General Hospital with cardiovascular symptoms.

In other localities, left ventricular strain would be an even more frequent cause, relatively, of right ventricular hypertrophy.

This study adds weight to the recent work of Harrison[5] in emphasizing the "back pressure" theory of congestive heart failure. We believe also that it adds emphasis to left ventricular strain and weakness as a cause of more far-reaching effects than is commonly appreciated, and that strain, hypertrophy, and failure of the right ventricle are dependent more frequently upon the same processes in the left ventricle, which have preceded by some weeks or months, than they are upon other factors. We have, then, further corroboration of the importance of the recognition of the effects of left ventricular strain and of the conception of left ventricular failure, which have so long been neglected in English medical literature.

SUMMARY

Among 2,000 consecutive post-mortem examinations, 704 cases had hypertrophy of the right ventricle to the extent that the wall measured 5 mm. or more in thickness. In about one-fourth of these, no strain on either side of the heart was clearly evident. In 61 per cent of the remaining cases, the strain on the heart had been due to arterial hypertension, aortic valvular disease, or infarcts of the left ventricle, and no factor producing primary right ventricular strain could be found. Left ventricular strain was, then, the commonest cause of hypertrophy of the right ventricle.

Hypertrophy of the right ventricle was often found in cases with pure left-sided strain, regardless of the presence or absence of clear clinical evidence of failure of the left ventricle, but the presence of failure increased the degree of hypertrophy.

The degree of hypertrophy of the right ventricle was almost as great in cases with pure left-sided strain as it was when there had been primary right-sided strain.

A few examples of preponderant hypertrophy of the right ventricle were found in cases with pure left-sided strain in this series. Four of these had electrocardiograms showing right axis deviation. We have encountered two other similar cases, not in the series analyzed above.

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DISSECTING ANEURYSMS OF THE AORTA

With a Report of Five Cases*

Thomas M. Peery, M.D.
Charleston, S. C.

DISSECTING aneurysms are supposed by most clinicians to be rare conditions, of interest only to pathologists. In 2,763 autopsies at the Roper Hospital from Jan. 1, 1914, to July 1, 1935, there have been five cases of dissecting aneurysm of the aorta, an incidence among those autopsied of 0.18 per cent. Shennan[7] reports 11 cases in a total of 1,922 post-mortem examinations at Aberdeen from January, 1918, to December, 1932, an incidence of 0.57 per cent. As a matter of fact, dissecting aneurysms are probably more common than even pathologists realize, as it is likely that not a few cases of sudden death, commonly ascribed to "a heart attack" and not autopsied, are of this nature.

Shennan, in his admirable survey of the subject in 1934, collected 297 cases of dissecting aneurysm of the aorta from the literature, including the famous case of George II. A few cases of dissection have been reported in the pulmonary artery and a few in peripheral vessels.

FACTORS LEADING TO DISSECTION

Most of the reported cases that are available for study, and in which case records are satisfactory, give a previous history of hypertension, and cardiac enlargement is usually present.

Disease of the aortic walls is generally believed to be the most important factor predisposing to dissection. This is usually of the nature of an atherosclerosis. As is commonly known, atherosclerosis does its greatest damage to the intima and the inner layers of the media, leaving the outer portions of the media and the adventitia relatively uninvolved. On the other hand, syphilis usually does its greatest damage in the adventitia and the outer coats of the media with relatively little actual weakening of the intima, in spite of its altered appearance. Thus herniation of the inner coats through the diseased outer ones, with the formation of a saccular aneurysm, is the common thing in syphilis of the aorta, while a rupture of the diseased inner coats and a dissection inside of the healthy outer coats occurs in atherosclerosis.

With this background of increased blood pressure and arterial disease is almost always associated an immediate precipitating factor further to elevate the blood pressure.

Physical trauma is commonly given as the precipitating factor, but, as Shennan has pointed out, a severe blow to the chest or the abdomen would be more likely to lead to immediate rupture of the aorta.

*From the Department of Pathology, Medical College of the State of South Carolina.

Shennan suggests that in many cases the precipitating factor is "internal trauma," such as straining, undue emotion, etc., which may raise the blood pressure sufficiently to begin dissection in an aorta whose media is already diseased. In a case reported by White and his associates,[8] a lawyer trying a case in court was suddenly seized with agonizing pain. Other cases have occurred in patients with prostatic obstruction as they attempted to urinate or in patients during an epileptic convulsion. It is conceded that none of these circumstances can so raise the blood pressure that rupture of the intima of a normal aorta can occur.

Fig. 1.—Longitudinal section of normal aorta at ligamentum arteriosum. Note fibrous band passing through media toward intima, and spreading out between fibers of media. This natural defect tends to weaken the aorta at this point. (× 52.)

SITE OF RUPTURE

Contrary to what would seem to be the case, the original rupture commonly does not occur in immediate relation to an atheromatous plaque or ulcer. Of the fifteen cases examined personally by Shennan, only four showed an immediate relation to atheromatous patches, and none was in the base of an atheromatous ulcer. Instead, the site of rupture appears to be determined by mechanical factors which tend to submit the aorta to particular strain at certain points. In Shennan's collected cases, most of the intimal tears were either in the ascending arch of the aorta or at the site of the ligamentum arteriosum. Shennan believes that ". . . . when the aortic valves have closed, the abrupt recoil of diastole must bring about a longitudinal stretching of the ascending aorta, and

must forcibly drive the aortic valve, along with the origin of the aorta, downward and away from the transverse part." Hence, the intimal tears in the ascending aorta are usually transverse. On the other hand, ". . . . at the ligamentum one passes from the relatively free arch to the relatively fixed descending aorta, and . . . . at every pulsation there is a hingelike motion at the junction of the two. This implies a local enhanced tendency to wear and tear, and to degeneration of the wall."

From the study of several aortas that were thought to be normal both grossly and microscopically, it is apparent that the aortic wall at the insertion of the ligamentum arteriosum is weaker than elsewhere. This is anticipated when it is recalled that the old ductus arteriosus must be obliterated, a process which necessarily requires fibrous tissue replacement. At the site of passage of this band through the walls of the aorta, a dimpling of the intima of the aorta can almost always be made out grossly, and microscopically a band of fibrous tissue passes from this dimple through the coats of the aorta, tending to spread out in the deeper reaches of the media (Fig. 1). While this is probably the important reason for the predominance of dissecting aneurysms at this point, it is probable that the fixation of the aorta at this point is also a factor.

CHANGES IN THE AORTIC WALL LEADING TO DISSECTION

Of the specific changes in the aortic wall that precede dissection, it is probable that degeneration and inflammation may both play a part in different cases. Those cases associated with atherosclerosis are usually of a degenerative nature. Shennan has pointed out that "deleterious agencies," acting to produce degeneration of the aorta, would be more likely to affect the innermost layers of the media than the other portions, because of their poorer blood supply. Microscopically the lesion consists of the various changes commonly noted in the intima in atherosclerosis (i.e., fatty deposits, hyalinization, calcification) plus rather characteristic medial changes. The regular parallel arrangement of the muscular and elastic laminae is irregularly interrupted by fibrous tissue, which often appears hyaline and degenerated. This tissue runs obliquely or transversely in the media. Occasionally a vas vasorum will be noted in close relation to the fibrous fault, and occasionally this small vessel will show evidence of intimal proliferation, with narrowing of its lumen. In such cases it is probable that the fibrous tissue in the media represents an area of insufficient blood supply. In other cases no disease of the vasa can be made out, and then the medial change is indefinitely assigned to toxic or metabolic causes. Occasionally small areas of necrosis are noted in the media in cases of atherosclerosis; these are usually crescentic in shape, contain a number of polymorphonuclear and round cells, but lack other evidences of inflammation. Usually these areas appear to be a result of infarction of the aortic wall, from obliterated vasa vasorum.

In the reported cases in which inflammation (and not primary degeneration) is thought to be the important agent, syphilis is the commonest inflammatory process. In 218 cases of recent dissection collected by Shennan, syphilitic mesaortitis was thought to be present in 21. In the Roper Hospital, where negro patients have a high syphilis rate, it appears that syphilitic mesaortitis is more commonly the background for dissection than Shennan's figures would indicate. Of the five well-developed dissections reported here, one was definitely syphilitic and an-

Fig. 2.—Case 27730. Medial necrosis of aorta in syphilis. Such a lesion as this probably exists when syphilitic aortitis is the background for dissection, rather than the usual scarring of the outer coats of the media. (× 20.)

other may have been of that nature. There are several other sections of syphilitic aortas in our files in which short dissections have occurred, and others in which it would be very easy to imagine that a dissection could take place. Two of these deserve description.

CASE 27730:35-100, a sixty-year-old negro male, dying of cardiac decompensation. The aorta was irregularly dilated, especially about the orifice of the innominate artery, where there was a small funnel-shaped aneurysm. Grossly the intima was very roughened and nodular, and the adventitia shared in the general thickening of the walls. Microscopically, the adventitia and media showed large perivascular collec-

tions of lymphocytes, and the adventitia was greatly thickened and hyaline. Much more striking were several crescentic areas of necrosis in the innermost layers of the media, where muscle and elastic tissue were disintegrated and many polymorphonuclear cells were collected (Fig. 2). The defects thus formed extended transversely about the aortic wall, and gave the appearance of crescentic abscesses between the intact fibers of the media. There was no evidence of hemorrhage. A small amount of calcification was noted about the necrotic area. The overlying intima was not calcified, although somewhat thickened and hyaline. This was judged to be a syphilitic aorta, with acute necrosis; the blood Wassermann reaction was four-plus.

Another aorta, that of a fifty-year-old negress (28462:35-113), showed even more striking changes. Grossly the aorta showed the nodular and striated thickening of the intima about the commissures of the aortic valves, with valvular insufficiency, commonly associated with syphilitic aortitis. Microscopically it was evident that a

Fig. 3.—Case 28462. Extensive medial necrosis of aorta, with small dissection. This section shows evidences of syphilitic aortitis. Note narrowing of vas vasorum in adventitia. (× 12.)

small dissection had occurred in the walls (Fig. 3). The media was extensively distorted by bands of fibrous tissue running obliquely and transversely to the normal muscular and elastic laminae. In several fields, these fibrous bands extended up to and involved the intima. Within one of these fibrous bands an old area of hemorrhage was noted. The periphery of the dissecting area showed a granular deposit of calcium. There was no evidence of the formation of an endothelial lining about the clot. Deeper in the media, and in the adventitia, were large collections of lymphocytes and plasma cells, usually in a perivascular position, and being so closely packed as to suggest miliary gummas. The blood Wassermann reaction was four-plus.

From a study of these two aortas, one with a very small old dissection, the other without dissection but certainly prone to it, it appears that

mesaortitis can cause dissecting aneurysm. However, the distortion of the muscular and elastic laminae of the media that occurs in the common form of syphilitic mesaortitis probably resists the splitting of the media necessary for dissection, as has been pointed out by Gager[3] and by Shennan. If dissection should begin, it seems doubtful that it would extend far along the aorta. Further, it seems likely that when the aortic disease associated with dissecting aneurysm is syphilitic, there must be medial degeneration and necrosis similar to that seen in dissecting aneurysms whose background is atherosclerosis.

A discussion of the factors leading to dissection would be incomplete without reference to the work of Babes and Mironescu.[1] In 1910 they stated that, while increased blood pressure usually causes intimal changes, it may cause degenerations of the media with breaks in that coat. Quoting: "These medial splits are certainly usually a direct consequence of the dilatation [of the aorta] and accordingly take place perpendicularly to the surface of the aortic wall, but the degeneration of the media may, in consequence of dilatation of the inner components of the wall, lead to splittings of the layers parallel to the surface of the aortic wall. . . . Then after the degenerated intima had burst as a result of trauma, the blood was poured between the already split medial layers." However, it would seem very unlikely that the inner coats of the aorta could dilate without the outer coats dilating to a proportionate extent. Consequently it would appear that such a force, acting on the inner coats to produce perpendicular tears, would act on the outer coats in the same way, giving a direct rupture without a dissecting split in the media.

SYMPTOMS

The usual symptom of onset is a sudden intense pain in the thorax, frequently knifelike in character, and generally radiating to the back or shoulders. A sensation as of suffocation commonly comes on early and may be followed by collapse or even coma. The blood pressure usually remains elevated, as contrasted with the fall usually encountered in coronary occlusion. A change in the character of the pain, or an extension of the pain, as down an extremity or to the abdomen, suggests that dissection is progressing in the direction indicated by the new radiation of pain. The usual symptoms of mediastinal compression, such as difficulty in swallowing, inequality of the pupils, etc., may be present. When extension occurs along the iliac or brachial arteries, with resultant narrowing of the lumina of these vessels, cyanosis, coldness, loss of pulse or numbness may develop, as in the case of Kellogg and Heald.[4] Such a state of affairs, occurring suddenly and associated with pain in one with hypertension, will occasionally permit the diagnosis to be made ante mortem, as pointed out by Crowell.[2] Other less common symptoms may be blindness, hemiplegia, etc., and when these are present, extension has usually occurred along the carotids.

Very rarely has the diagnosis been made during life, and none of the cases here reported was so diagnosed.

"HEALING" OF DISSECTING ANEURYSMS

While it is generally thought that the condition is always fatal, such is not the case. Kellogg and Heald state that 80 per cent die within a few days, but that the remaining 20 per cent have a good chance of recovery. If external rupture of the dissecting channel does not occur, with hemorrhage into the body cavities, it is easy to conceive that recovery can take place. All but one of the collected cases of recovery from the initial dissection showed two ruptures, one from the aortic lumen into the walls, and another from this new channel back into the lumen of the aorta. When such a rupture has not occurred, there is further extension of the dissection with each systole and imminent danger of rupture to the exterior. This danger is much greater, of course, if the blood pressure remains at the level at which the original rupture and dissection occurred. If rupture back into the lumen of the vessel occurs, and the blood pressure is kept at a low level, the new channel may become coated with endothelium, and, while it is by no means a perfect vessel, it will function. Evidence of healing of dissecting aneurysms is found in those cases where old channels, lined by endothelium, are found within the walls of the aorta. Seventy-four such cases have been found by Shennan in the literature, and another is added in this report. Of the 74 cases collected by Shennan in which healing had occurred, many were thought to be several years old. Samson's case[6] was thought to be of five years' duration. The case included briefly in this report (and reported more completely elsewhere[5]) is thought to have been of fifteen and one-half months' duration. In such cases, death is usually from cardiac failure, chronic nephritis, or intercurrent infection.

CASE REPORTS

CASE 1 (56:14-11).—R. B., a twenty-two-year-old negress, was first admitted to the Roper Hospital on Dec. 16, 1913, and discharged Dec. 30, 1913. She was readmitted on Jan. 29, 1914, and died Jan. 31, 1914.

The charts give little information. The first admission was apparently for a gynecologic condition. The blood pressure was not recorded. On the second admission she was complaining of severe pain in the epigastrium, which was only slightly relieved by large doses of morphine. The temperature was subnormal, the pulse rate 120 per minute, respirations 22 to 36 per minute. The blood pressure was not recorded. She died soon after admission.

Autopsy was performed a few hours after death, and the heart and aorta were preserved in the Pathological Museum. Examination of the mounted specimen showed a moderately enlarged heart, weighing about 500 gm. The coronary arteries were normal. The myocardium of the left ventricle measured 1.75 cm. in thickness. The valves were normal. The intima of the aorta showed a number of rounded, raised plaques, chiefly about the mouths of the small vessels. Most of these plaques were hyaline, but a few were calcified. There was considerable wrinkling of the intima, especially between plaques that were near each other.

At the orifice of the innominate artery there was a small saclike pouching of the walls, but the intima here appeared the same as elsewhere. At the beginning of the descending aorta, and corresponding to the site of attachment of the obliterated ductus arteriosus, there was a crescentic tear in the intima (Fig. 4). This began as a longitudinal rent proximally, passing across a depressed area in the intima (which was the remnant of the aortic end of the ductus), and then bent in a uniform arch to end as a transverse tear across the most inferior and most concave portion of the arch, partially surrounding at this point a small hyaline plaque. The whole tear was about 2.5 cm. in length. At the middle of this crescentic tear there was

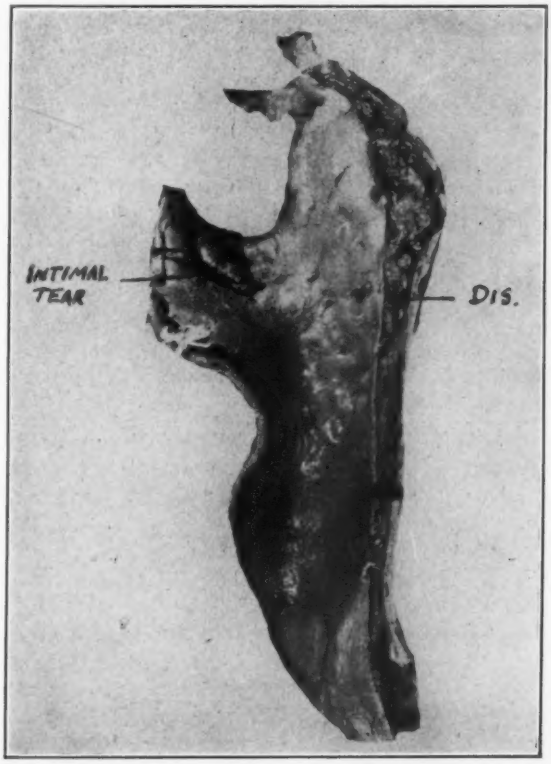

Fig. 4.—Case 1. Descending portion of thoracic aorta, showing intimal tear and dissection between layers of media.

another which crossed the first at a slight angle; this appeared to be a secondary tear, and was about 2 cm. in length, the point of intersection exactly overlying the intimal depression mentioned above. Beneath this, the media was separated into two layers, the separation appearing grossly to be between the middle and outer thirds of the muscle coat. Between these layers a strikingly uniform blood clot completely surrounded the aorta, and was generally about 0.5 cm. in thickness. The dissection extended proximally for about 2 cm. and distally as far as the specimen extended. (The description written at that time stated that the dissection extended to the diaphragm.) The adventitia was somewhat thickened in a uniform fashion. Posteriorly, at a point about 5 cm. distal to the intimal tear, the dissection was about 2 cm. thick, and the extravasation extended into the adventitia and nearby structures, beneath the pleura over the roots of both lungs. At this

thickest point there was a large ragged ruptured area where the dissecting sac communicated with the pleural cavity, where the fatal hemorrhage occurred.

Sections from the aorta at the site of the dissection show a somewhat thickened hyaline intima, and a greatly damaged media. Muscle and elastic tissue fibers are interrupted several times in each low-powered field by infiltrating fibroblasts, and the fragments of muscle are hyaline and degenerated.

Numerous lymphocytes and plasma cells are seen at a little distance from the dissected area, which, with the numerous fibroblasts, indicate that the patient lived for some little time after the dissection began. Most of these cellular changes are taken to be secondary to the dissection rather than the pathologic background for the dissection. Sections from the arch proximal to the dissection show prominent but small slitlike channels that are taken to be dilated lymphatics. They are in close proximity to the vasa vasorum and are lined with endothelial cells. About these small channels and about the vasa vasorum are numerous plasma cells and lymphocytes, occurring in small clusters in which fragments of a collagen-like material are frequently found. Other portions of the media do not show these slitlike spaces, but localized areas of fibrosis, extending both parallel to, and across, the regular fibers. Intimal changes away from the dissection are not prominent, there being merely a mild degree of hyalinization, without fatty deposits or calcification. This lack of evidence of atherosclerosis, together with the youthfulness of the patient (twenty-two years), makes rheumatic aortitis a possibility, although Aschoff bodies cannot be demonstrated in the myocardium and although the valves are free from disease. In some areas the changes are such as are commonly found in syphilitic aortitis. At any rate, it appears that the medial disease in this case is more of an inflammatory nature than a primarily degenerative one.

CASE 2 (12397:31-125).—P. M., a forty-nine-year-old negro, a laborer, was admitted to the Roper Hospital on May 7, 1931, and died on May 19, 1931. Symptoms of congestive heart failure had been present for six months, growing progressively more severe.

He had a penile sore in 1917 and a "stroke" in 1930, but the effect of the latter had been only temporary. There had been no other illnesses.

On examination his temperature was 98.4° F., pulse rate 114 per minute, respirations 28. The blood pressure was 216/140. Chest examination showed scattered râles over the bases of both lungs, but no other abnormalities. The mediastinum was normal on percussion. The apex was noted by auscultation to be in the sixth interspace, just to the left of the nipple line. Both the aortic and the pulmonic sounds were accentuated, but the other sounds were normal and there were no murmurs. The radial arteries felt thickened. The pulse was regular. The Kolmer and Kahn tests of the blood were negative.

On digitalis therapy, moderate restriction of fluid intake, and diuretics, there was definite improvement, with disappearance of the edema and with much less dyspnea. On May 18 he was suddenly seized with a severe pain in the left side of the chest, markedly exaggerated by deep breathing. Simultaneously the pulse rate dropped to 48 per minute, and dyspnea became severe. A quarter grain of morphine relieved the pain somewhat, and the patient dropped off to sleep (or passed into coma?), although he groaned continuously. The skin became cold and clammy, the pulse rate remained slow and became irregular, and he died fourteen hours after the onset of the pain. The temperature was subnormal for several hours before death.

Autopsy was performed the day after death. The heart weighed 600 gm. and the left ventricle was markedly hypertrophied. There was a slight pericardial effusion, without evidence of bleeding into the sac. The lungs and liver were con-

gested. The intima of the aorta was irregularly thickened, rough and hyaline, and was moderately dilated in the ascending portion of the arch. Three transverse linear breaks resembling incisions were noted in the descending portion of the arch, and one of these communicated with a longitudinal sac in the wall, which had its base on the pulmonary artery, and contained a fresh thrombus. Unfortunately the specimen was not more fully described in the records and was not preserved. The description sounded like a rather small dissection, which probably occurred at the time of the onset of the severe pain in the side. As it had not ruptured, it probably would not have been fatal if the patient had not already been in poor condition.

Microscopic sections from the aorta show an irregularly nodular intima, the nodules composed of a loose, myxomatous fibrous tissue in which numerous small fat droplets are evident. Deeper in the media irregular breaks are noted, confined to the inner two-thirds of the media, in which the medial fibers are completely dis-

Fig. 5.—Case 2. Marked medial necrosis, with complete disruption of muscular and elastic fibers. Not from the area of dissection. This aorta showed unmistakable evidence of syphilis. (× 80.)

rupted. The ends of the muscular and elastic fibers are frayed out and hyaline. One of these faults occupies almost the whole of a low power microscopic field and is filled with a loose, fragile-looking, young fibrous tissue in which are large numbers of mononuclear and polymorphonuclear cells (Fig. 5). The outer layers of the media, even at this point of greatest involvement, appear quite normal, and their muscular and elastic fibers pursue their normal circular course. Elsewhere in the media smaller cellular accumulations are noted, composed of mononuclear and plasma cells confined to small areas about vasa vasorum and having the appearance in some areas of miliary gummata. While the sections at hand now do not include the dissection proper, it is believed that dissection occurred through a lesion similar to the large one described above, the intimal covering of which appeared very delicate. This aorta appears to be definitely syphilitic.

Case 3 (21487:34-110).—A. W., a negro male of thirty-three years, was first admitted to the Roper Hospital in June, 1922. A high thigh amputation was done

for a ruptured aneurysm of the femoral artery, the nature of which is not clear from the record. There was no history of trauma. The blood pressure was 190/120.

On his final admission to Roper Hospital, on May 23, 1934, he was forty-five years old. His symptoms were those of congestive heart failure of about four months' duration. He had had a sore on his penis many years before.

On examination, the heart was greatly enlarged, and the second aortic sound was loud and ringing. The arteries were palpably thickened, and the blood pressure was 220/170. Pulmonary congestion, a large tender liver, ascites, and edema were noted. The respirations were 28 per minute. The urine showed a specific gravity of 1.022, a heavy trace of albumin, occasional hyaline casts, and occasional

Fig. 6.—Case 3. Small dissection of ascending aorta, with rupture into pericardium. Viewed from outer surface of aorta.

red and white blood cells. At no time did he complain of pain, only of dyspnea and a general feeling of discomfort. No improvement was effected by sedation, diuretics, and digitalis. On May 31, 1934, without an outcry, he suddenly slumped back in bed, became pulseless, and ceased to breathe.

Autopsy was performed forty-eight hours after death. There was moderate edema of the left leg. The pleural sacs were dry. The lungs showed merely passive congestion. The pericardial sac contained a large blood clot estimated to represent about 1,500 c.c. of blood. The heart was greatly enlarged, weighing 960 gm., and was very pale. The myocardium of the left ventricle was 2.5 to 3.0 cm. in thickness. The mitral, tricuspid, and pulmonary valves all appeared normal. Beginning just above the aortic cusps on the anterior surface, the intima was irregularly elevated

and small deposits of fat were noted, but no definitely calcified plaques could be found. A little higher up in the ascending aorta definite longitudinal wrinkling of the intima was noted with numerous hyaline nodules. The adventitia was also definitely thickened. In the upper portion of the part showing the atheroma and extending upward to the part that appeared grossly to be syphilitic, there was a linear opening in the intima 3 cm. in length. This was on the anterior surface and was curved so as to form a barely evident "S" In its center it gaped about 0.5 cm., and at its upper end it showed a double split, forming a "Y," each limb of which was very short. This tear extended into the media, dissecting there in a circular fashion so as almost to surround the aorta, and extending downward along the right coronary artery for a short distance. The dissection continued distally for about 3 cm., lying in the very outer coats of the media (Fig. 6). Near the

Fig. 7.—Case 3. Complete disruption of media in atherosclerosis. Note marked narrowing of vasa vasorum. (This defect was one of several; it was not the site of the fatal dissection.) (× 18).

center of the dissected area, and corresponding to the most gaping portion of the tear in the intima, this tear extended through all the coats of the aorta. The openning through the adventitia was about 4 mm. in diameter, and its edges were rough and gaping. It was this extension of the tear that gave rise to the hemopericardium and the sudden death. At the same level as this large tear, but on the right side of the aorta, there was a roughly V-shaped tear, apparently in the media only, and covered over by a thin layer of intima. The angle of the "V" was directed upward and to the right, and the limbs extended downward between the commissures of the right posterior cusp of the aortic valve. In the region of this V-shaped fault there was no evidence of dissection, either recent or old.

Sections through the aorta at the site of the dissection show large defects in the media, where the normal circular muscle bands are replaced by hyaline or necrotic whorls of tissue. Hemorrhage has occurred into the media at the site of

this fault, and dissection is evident even between the layers of media that appear normal. The intima overlying the defect is somewhat thickened and hyaline, but by no means elevated to form a plaque and there is no evidence of calcification. A little to one side of the actual medial defect the intima is broken through, and the blood was apparently admitted to the medial defect from this intimal cleft. There are a few cells in the line of cleavage, and in the outer layers of the media and in the adventitia are larger collections of cells. These latter cells are largely fibroblasts with a small spattering of lymphocytes among them. The round cells do not appear to have a definite perivascular arrangement, and there are none of the plasma cells so commonly seen in syphilitic aortitis (Fig. 7).

This case showed gross features in the aorta very strongly suggestive of syphilis as well as of atherosclerosis, but the microscopic appearance is that of an aorta degenerated from atherosclerosis. The aneurysm of the femoral artery in this case, rupturing in 1922, may have been a dissecting aneurysm, but that cannot be definitely stated. At autopsy there was a widespread atherosclerosis in all the larger arteries.

CASE 4 (21990:34-127).—(This case is reported in more detail elsewhere.) J. F., a negress, was first seen at the age of forty-six years in the Shirras Dispensary. At this time (1927) the blood pressure was 220/130. She was admitted to the Roper Hospital on March 17, 1933, complaining of severe pain in the epigastrium, radiating through to the back, which had come on suddenly about eight hours before. Vomiting, slight hemoptysis, and definite hematuria came on a few hours later.

On examination she was in acute distress. The temperature was subnormal, pulse 90 per minute, respirations 24, blood pressure 190/110. The apex beat was in the fifth interspace 2.5 cm. to the left of the midclavicular line. The heart tones were normal, and no murmurs were heard. The arteries were markedly sclerotic. There was marked tenderness in the epigastric region and in both lumbar regions, with moderate tenderness in the suprapubic area. The voice was quite hoarse. On laryngoscopic examination a partial paralysis of the right vocal cord was noted, with imperfect approximation. A few hours after admission the urea nitrogen was 21 mg. per 100 c.c., and this gradually rose to a peak of 121 mg. four days after admission, after which it gradually fell to 13 mg. on the day of discharge. The urine contained grossly evident blood for five days after admission. Leucocytes on the night of admission numbered 28,100, with 79 per cent polymorphonuclears. The hemoglobin was 85 per cent (Dare). The leucocytes gradually fell to 7,600 with 65 per cent polymorphonuclears on the day of discharge, the hemoglobin then being 50 per cent (Dare). The blood Kolmer and Kline tests were negative. The temperature rose to 101.4° F. on the day after admission, gradually falling to normal after one week. The pulse varied below 130, being highest on the second day after admission, and gradually tending to fall to normal. The blood pressure was constantly elevated, although subject to variations. An x-ray of the chest two weeks after admission showed "an unusually large aneurysm of the entire aortic arch," without noteworthy cardiac enlargement.

Morphine was required for the relief of pain for several days, but improvement was constant, and at the time of discharge forty-two days after admission the only complaints were pain, weakness, and numbness in the right foot and leg.

On June 25, 1934, J. F. was readmitted to the hospital, complaining of shortness of breath, and difficulty in swallowing, talking and breathing. The blood pressure was 192/140. Coarse moist râles were heard over both lung fields. The heart was markedly enlarged and the sounds were of fair quality. A loud, high pitched systolic murmur was heard, of maximum intensity at the aortic area and at the apex. There was a tambourlike second aortic sound. The abdomen was negative. Moderate edema of both feet was noted, especially the left. An x-ray plate of the chest, taken the day after admission, showed little if any change in the appearance of the

"aortic aneurysm," although the heart had enlarged greatly in the interim, now measuring over 7 inches as compared with 5 inches in April, 1933.

The urine contained 3-plus albumin but no casts. The hemoglobin was 62 per cent (Dare). The blood Kolmer and Kline tests were negative. She showed little improvement, gradually became stuporous, and died on July 1, 1934.

Autopsy was made twenty-four hours after death. There was marked nephrosclerosis and a large old infarct of the left kidney. Cardiac hypertrophy was moderately advanced, and there were evidences of congestive heart failure. The coronary arteries were patent and appeared normal. Lobular pneumonia was present.

Viewed from the exterior, the aorta showed a rather uniform dilatation beginning in the distal portion of the arch and extending to the termination of the aorta. On opening the aorta the true aortic channel was almost completely surrounded by a second vessel, crescentic in shape, which also contained blood. This false channel extended proximally into the descending portion of the aortic arch, while distally it went well out into both iliac arteries. The true nature of the condition was not realized at the time of autopsy and the lower extent of the dissection was not determined; it extended more than 6 cm. from the bifurcation, where both iliacs were severed. The communication between the two channels and the site of the rupture, which apparently occurred fifteen and one-half months before, was at the termination of the ligamentum arteriosum. The orifice connecting the two channels was a slightly gaping, slitlike one, 1.5 cm. in length, its direction almost transverse, but with its posterior end directed slightly downward. Proximal to the dissection, the intima showed merely a few fatty deposits, and no calcification or ulceration. There was no abnormal thickening or wrinkling of the intima or adventitia. There was no grossly evident lesion of the intima near the site of rupture. The intima of the false channel was irregularly roughened and wrinkled. Generally the lining was paler than that of the true channel, but a few small fatty deposits were noted in the false channel. The false vessel surrounded the true one except on the posterior surface where the two walls merged. Numerous intercostal arteries were torn across by the false channel. The renal, the pancreatic, and the superior mesenteric arteries showed false channels in their walls, continuous with the channel in the walls of the aorta, and they also contained blood. Thrombi were noted in the lumen of several of these secondary false vessels, and these thrombi extended into the false aortic channel to surround the orifices of these smaller vessels.

Sections from the area of dissection show that the false vessel lies between the middle and the outer thirds of the media. The media, as included in the walls of both channels, is extensively degenerated, and the elastic tissue is fragmented and quite scarce. The intima of the new channel is very dense and thick, the media thin and apparently inefficient, the adventitia greatly thickened.

Sections taken from the aorta proximal to the splitting of its walls show numerous "faults" in the media, interrupting the normal circular fibers and tending to spread out somewhat between the layers of the media. At these faults the muscle is degenerated and the elastic tissue has completely disappeared, leaving in its place a loose, hyaline fibrous tissue containing a number of endothelial cells lining small sinuses, apparently of lymphatic nature. This tissue gives the appearance of being quite fragile. In no section is there any suspicion of syphilitic disease. As a matter of fact, atherosclerosis is also at a minimum, as there seems to be little intimal degeneration even where medial defects are quite prominent.

CASE 5 (24781:35-9).—T. G., a negro of about forty years of age, was not admitted to the hospital, and hence his history is far from complete. It was learned that he had had a heated argument with his wife, after which he left the house in a fit of rage. As he passed through the yard, he suddenly fell and in a few minutes was dead. Because of the unusual circumstances about the case, the wife refused to

answer questions about her husband's state of health, thinking that she was to be prosecuted for his death. But, curiously enough, the wife requested an autopsy.

Autopsy was performed the day after death (Jan. 13, 1935). Opening the thorax revealed that the left pleural cavity contained about 3,000 c.c. of partially clotted blood. The heart and entire aorta weighed 435 gm. The heart itself was entirely normal. The ascending portion of the aorta was smooth and elastic and quite resistant to tearing. In the transverse portion of the arch, adjacent to the orifices of the great arteries, several atheromatous plaques were noted in the intima, yellow and fatty at their periphery, hyaline toward their center, with a minimal amount of calcification. Just lateral to the origins of the first and second left intercostals, about 2 cm. from the termination of the ligamentum arteriosum, was an

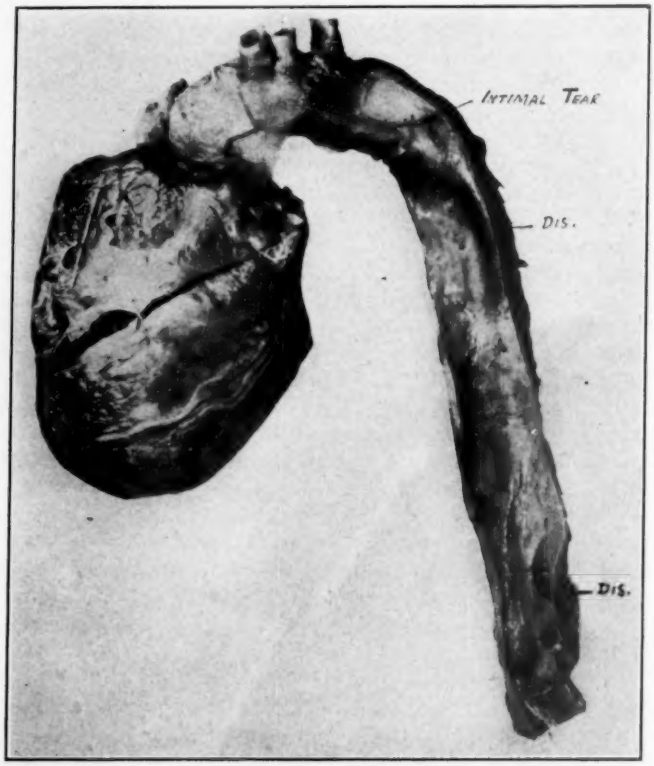

Fig. 8.—Case 5. Intimal rupture just to one side of a small atheromatous plaque, with dissection in the adventitia, and rupture into the left pleural sac.

intimal plaque about 7 mm. in diameter, with very slight calcification. At its left border this plaque was elevated and torn, giving a V-shaped tear in the intima, and it was through this that rupture occurred. Arising at this site and extending in both directions in the axis of the aorta was a blood clot which grossly appeared to lie between the media and the adventitia (Fig. 8). At its origin the clot was 4 mm. in thickness and completely enveloped the aorta, although it was much thinner opposite the rupture. Proximally the dissection extended as far as the reflection of the pericardium, where it abruptly terminated. Dissection continued along the great arteries arising from the arch, especially the left subclavian, for a distance of several centimeters. Distally the dissection completely enveloped the aorta as far as the origin of the celiac axis, where it was 1 mm. thick. Just beyond this, the

dissection ended in an irregular margin. The point of rupture of the dissecting sac was just over the rupture in the intima. Here the adventitia was definitely torn, and the edge of the sclerotic plaque in the intima protruded through the adventitial opening. (Doubtless, in such a case as this, where a very thin-walled sac is formed, only a very short interval exists between the time of the beginning of the dissection and the rupture of the dissecting sac.)

Microscopic sections from this aorta show that the intima is only slightly thickened and somewhat hyaline, with a finely granular deposit of calcareous material scattered about, but with few definite calcareous plaques formed. In most areas the media appears entirely normal. In several areas, however, the muscle fibers are definitely degenerated and the elastica has lost its regular arrangement. The adventitia is normal both in thickness and general appearance. The dissection is largely in the adventitia, between its component layers; in some sections the separation is between the media and adventitia, but in no field is the media itself split. There is no suspicion of syphilitic disease.

COMMENT

From the data at hand, a few things can be gleaned that may be of assistance in the clinical management of a case in which the diagnosis can be made during life. In the event of a recent dissection, it would seem essential to lower the blood pressure, preferably by venesection followed by agents which may act over a longer period of time. This may serve to arrest further dissection. It goes without saying that absolute rest is all-important, as the danger of complete rupture remains grave for many days after beginning dissection.

In the event that the patient recovers from the period of actual dissection, it is probable that he will be handicapped by the loss of aortic elasticity, thus throwing upon the heart the entire burden of propulsion of the column of blood. This is evidenced by the rapid development of signs of decompensation in Case 4, following establishment of the new channel. Further, as the "healed" channel is still prone to complete rupture due to imperfections in its walls, the patient is not out of danger even when he has survived active dissection. With this in view, a patient who has recovered from his dissection must be handled in the same way as any cardiac cripple.

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THE SIGNIFICANCE OF AN UPRIGHT OR DIPHASIC T-WAVE IN LEAD IV WHEN IT IS THE ONLY DEFINITE ABNORMALITY IN THE ADULT ELECTROCARDIOGRAM*

JOSEPH EDEIKEN, M.D., CHARLES CHRISTIAN WOLFERTH, M.D., AND FRANCIS CLARK WOOD, M.D.
PHILADELPHIA, PA.

SINCE the value of chest leads in the study of coronary occlusion was demonstrated in 1932,[1] many observations have been made concerning them, and their advantages and limitations have become more clearly defined. In a certain group of cases the limb leads furnish all or practically all the diagnostic information. Lead IV shows no deviation from normal. Examples of this are seen in many cases of healed posterior infarction. In another group of cases abnormalities are found in both the limb leads and Lead IV. In this group the findings in Lead IV may be (a) superfluous (b) of considerable assistance in clarifying or intensifying a diagnostic impression gained from limb leads, or (c) of primary importance. In a third group Lead IV shows significant abnormalities, when the limb leads are normal. For purposes of evaluating the benefits to be derived from taking chest leads, careful study of this third group seems indicated. The question is: If an abnormality appears in Lead IV when limb leads are normal, is it significant of heart disease or is it misleading?

The present paper is based on a group of twenty-six adult cases in which the T-wave in Lead IV was upright, or diphasic with a definite upright component. In other respects this lead was normal. Thirteen cases (shown in Table I) had no significant electrocardiographic abnormality in the limb leads: None of these thirteen had T-waves in either Lead I or Lead II which were less than 2 mm. in amplitude, and none showed left axis deviation of more than 10 degrees, according to the formula of Carter, Richter, and Greene.[2] Case 10 had a Q_3 wave but was included in this group because the heart was transverse in position.[3, 4] In the thirteen other cases (shown in Table II) the limb leads deviated from rigid normal standards, but the abnormalities were such that they could not be regarded as definite evidence of heart disease.

In all cases the chest lead was taken with the right arm electrode over the apex of the heart and the left arm electrode at the angle of the left scapula. T_4 was upright in 20 and diphasic with a definite upright component in 6. An additional chest lead from the apex to the left leg was taken in 22 of the 26 cases; in one (Case 3, Table I) the T-wave of this

*From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

TABLE I

CASE NO.	AGE	LIMB LEADS	T-WAVE IN CHEST LEAD	X-RAY OF HEART AND GREAT VESSELS	TYPE OF DISEASE
1	39	Normal	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris
2	50	Normal	Upright	Normal	Angina pectoris
3	50	Normal	Upright*	Normal	Angina pectoris
4	45	Normal	Upright	Normal; substernal thyroid	Angina pectoris
5	21	Normal	Upright	Heart moderately enlarged; aortic configuration	Rheumatic heart disease with aortic insufficiency
6	34	Normal	Diphasic	Heart slightly enlarged	Old coronary occlusion
7	47	Normal	Upright		Angina pectoris
8	58	Normal	Upright	Heart slightly smaller than average	Angina pectoris
9	55	Normal	Upright	Normal	Angina pectoris
10	55	Q_3 wave	Upright	Heart normal in size; transversely placed	Angina pectoris
11	46	Left axis deviation $\angle$ -9 degrees; otherwise normal	Upright	Normal	Old coronary occlusion
12	50	Left axis deviation $\angle$ -8 degrees; otherwise normal	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris
13	70	Left axis deviation $\angle$ -10 degrees; otherwise normal	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris

*In lead from apex to left leg T-wave was inverted.

TABLE II

CASE NO.	AGE	LIMB LEAD ABNORMALITIES	T-WAVE IN CHEST LEAD	X-RAY OF HEART AND GREAT VESSELS	TYPE OF HEART DISEASES
1	47	T_1 1 mm. high	Upright		Angina pectoris
2	51	T_1 1 mm. high QRS complexes 5 mm. in amplitude	Upright	Heart slightly enlarged	Old coronary occlusion
3	47	T_1 1 mm. high Q_3 wave	Upright	Normal	Angina pectoris
4	54	T_1 1.5 mm. high	Upright	Heart moderately enlarged	Angina pectoris
5	60	Slight slurring of QRS complexes	Diphasic	Heart moderately enlarged	Old coronary occlusion
6	52	Low T_2 Inverted T_3 Q_3 wave	Upright	Heart moderately enlarged	Angina pectoris
7	66	Low T_2 Inverted T_3	Upright		Paroxysmal cardiac dyspnea
8	54	T_1 0.5 mm. high	Upright	Normal	Angina pectoris
9	45	T_1 1 mm. high	Upright	Heart slightly enlarged	Angina pectoris
10	62	R_1 and $R_2 = 5$ mm.	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris
11	52	Left axis deviation $\angle$ -31 degrees; otherwise normal	Upright	Heart slightly enlarged	Angina pectoris
12	51	Left axis deviation $\angle$ -42 degrees; otherwise normal	Upright	Heart normal in size; aorta dilated and dense	Angina pectoris
13	26	Right axis deviation $\angle$ +128 degrees; otherwise normal	Upright	Heart moderately enlarged; pulmonary artery prominent	Congenital heart disease

lead was inverted while T_4 was upright; in the other cases the T-waves were similar in both these leads.

Roentgen ray study of the heart and aorta (film or orthodiagram) was carried out in 23 of the 26 cases (see Tables I and II). The heart was not enlarged in 14 cases; it was enlarged slightly in 4 and moderately in 5. The aorta was dilated and dense in 5 of the 14 patients who had no cardiac enlargement. Thus 9 of the 26 patients had no significant abnormality in either the roentgen ray examination or the electrocardiogram except the upright T-wave in Lead IV.

An examination of Tables I and II suggests that almost all adult cases showing an abnormal T_4 as the only significant finding, have angina pectoris, or a history of coronary occlusion. However, our data should not be regarded as conclusive evidence upon this point: almost all cases of coronary occlusion or angina pectoris which come to our clinic are studied with chest leads, whereas cases not suspected of having coronary artery disease are not always examined in this way.

The following control groups were studied to determine in them the frequency of an upright T_4:

A. Eighty-one children: Forty-eight had rheumatic heart disease; 33 had no evidence of heart disease. Upright T-waves were found in Lead IV in approximately 25 per cent of each group. Our observations[5] are in line with those of other observers;[6, 7] namely, upright T-waves in Lead IV may occur in children who have no evidence of heart disease.

B. Two hundred ninety-nine college students between the ages of sixteen and twenty-six years were examined with history, physical examination, orthodiagram, and electrocardiogram, with chest and limb leads. Only one showed an upright T_4. This patient had aortic insufficiency (Table I, Case 5). Three others had T-waves in Lead IV which were not strictly normal. The first had a blood pressure of 150/95, a heart rate of 110 per minute, and ventricular extrasystoles. T_1 was isoelectric; T_2 was slightly inverted; T_3 was definitely inverted; and T_4 was variable changing from plus 1 mm. to minus 1 mm. His tracing was repeated a few days later at which time T_1 and T_2 were plus 1 mm.; T_3 was diphasic; and T_4 was minus 1 mm. The second individual showed slight slurring of QRS; T_1 was plus 1 mm.; T_4 was diphasic, minus 2 mm. and plus 1 mm. After his electrocardiogram had been taken, he told us he had just run eight blocks to get to the appointment on time. Four days later, the tracing was repeated. The limb leads were much the same; T_4 had become normal (–3 mm.). The heart rate was 120 per minute in both the tracings. The third was an athlete with a small heart. T_1 was plus 1 mm.; T_2 showed a peculiar contour with a slight terminal inversion; T_3 was a "cove plane" wave, minus 1 mm.; T_4 was diphasic, minus 2 mm. and plus 1 mm. All the rest of the 299 college students showed a definitely inverted T-wave in Lead IV. In 2 it was minus 1 mm.; in 1 it was minus 2 mm.; in the rest it was

minus 3 mm. or more. These statements apply only to the chest lead taken with the anterior electrode placed to the left of the sternum, and below the third left interspace. When the electrode was placed over the base of the heart, or near the right border, upright T-waves were sometimes found.

C. Forty-five women between the ages of sixty-two and eighty-five years were studied in a home for old women, through the kindness and with the assistance of Dr. John H. Arnett. This group cannot be considered a strictly normal one since, among other things, the blood pressure figures exceeded 170 systolic or 100 diastolic in thirty-eight cases. One individual showed a nearly isoelectric T_4 and T-waves of low voltage in limb leads, not associated with other definite evidence of heart disease.* Ten cases showed a T-wave in Lead IV with an upright component. In nine of these, the limb leads were definitely abnormal. In the tenth, T_1 was low; T_2 was isoelectric; T_3 was inverted, and the patient suffered from cardiac complaints. These observations, though somewhat limited, suggest that there seems to be no tendency for T_4 to become upright with age, except in the presence of other evidences of heart disease.

DISCUSSION

The significance of an upright T-wave in Lead IV has been discussed by Levine and Levine.[8] They found T_4 upright in two patients who came to necropsy and showed no evidence of cardiac infarction. They write: "It is obvious, therefore, that an upright T-wave in Lead IV is of no value in the diagnosis of myocardial infarction. In fact, we have seen a positive T_4 occur as a transient phenomenon during bronchopneumonia, as have others, and as a permanent or transient finding under a variety of other circumstances, such as mitral stenosis, uremia and hyperthyroidism." They also found an upright T_4 in 9 of 100 cases of angina pectoris, in 7 of which "the customary three leads were normal." Their conclusion states that "upright T-waves in Lead IV were found when no infarction was present, and in fact where there was no significant heart disease."

Our opinion concerning the significance to be attached to an upright T-wave in Lead IV has been based upon an evaluation of the following observations: 1. The T-wave is notoriously unstable and is affected by a variety of factors. Digitalis, thyroid disease,[9] and intoxications of various types will cause it to change its direction. Exercise will cause significant T-wave inversion in limb leads in certain individuals, without evidence of heart disease.[9] In fact, there are certain persons, otherwise apparently normal, who have T-wave inversion in Lead II more or less

*In three other cases the T-wave was normal in Lead IV, but was isoelectric in a lead taken with the right arm electrode at the apex, and the left arm electrode on the left leg.

constantly. Thus one should expect to find an occasional subject without demonstrable heart disease, whose T-wave in Lead IV is upright. 2. A T-wave in Lead IV which was isoelectric, or diphasic with a small upright component, was seen in certain cases in Groups B and C, when the limb leads were abnormal, but where signs of heart disease were not absolutely definite. 3. A certain proportion of presumably normal children show an upright T_4. 4. Only one of 299 college students had an upright T_4 with normal limb leads. He was found to have rheumatic aortic insufficiency. 5. An upright T_4 was found in ten of forty-five women over sixty years of age. All ten had other evidences of heart disease. 6. The cases reported in this paper, in which an upright T_4 was the only definitely significant abnormality, showed, to say the least, a high incidence of serious heart disease. 7. We have not as yet seen an upright T_4 in an adult in whom we were at all confident that "there was no significant heart disease," unless the patient had received digitalis.

We feel that the following comments should be made concerning the statements of Levine and Levine[8]: In the first place, an upright T_4 occurs frequently in the absence of cardiac infarction. When present as an isolated finding, it is not a trustworthy sign of this lesion. However, in certain cases, it helps considerably to support this diagnosis, when changes in QRS are suggestive. Consequently, we disagree with the conclusion that it "is of no value in the diagnosis of myocardial infarction." In the second place, these authors make the statement that "upright T-waves in Lead IV were found . . . where there was no significant heart disease." In support of this statement, they refer to two patients, one who died of uremia, and the other who died of exsanguination from a bleeding peptic ulcer. They do not state the time interval between the taking of the tracing and the death of either patient. The electrocardiogram of the first patient shows an inversion of T_1 and T_2 (*Fig. 2F*).[8] The tracing of the second patient is stated to have shown an inversion of T_1, T_2, and T_3 (*Table III*).[8] No histologic studies of the heart muscle are presented. Now it is well known that definite poisoning of the heart muscle often occurs in uremia and that profound physiological changes may be produced in the myocardium by exsanguination. Moreover, T-wave inversions like those described in the limb leads of these two cases have been reported in very ill, and in moribund patients, presumably caused by pathological abnormalities of the heart muscle. Consequently, we interpret the statement of Levine and Levine[8] to mean that there was no primary, gross lesion of the heart in these cases, because they have not published evidence to establish the absence of considerable abnormality of the heart muscle. We stress this point since the simple statement that upright T-waves in lead IV were found where there was "no significant heart disease" might lead the reader to conclude that an upright T_4 is not dependable evidence of myocardial abnormality. As a matter of fact, our observations indicate that an

upright T_4 in an adult, obtained with the right arm electrode over the apex, is highly dependable evidence of such abnormality. Subsequent observation may bring to light an occasional case in which this sign is present when there is "no significant heart disease." However, no such case is known to us at present, in which digitalis has not been the probable cause of the T-wave change.

SUMMARY AND CONCLUSIONS

1. A group of 26 adult cases has been studied in which the only significant electrocardiographic abnormality was an upright T-wave in Lead IV or a diphasic T_4 with a definitely upright component. In 13 of these cases, the limb leads conformed to rigid normal standards; in the other 13, the limb leads showed slight deviations from normal, but nothing that could be interpreted as definite evidence of heart disease.

2. The cardiac diagnoses made in these cases were as follows: in 17, angina pectoris; in 2, questionable angina pectoris; in 4, old coronary occlusion; in 1, paroxysmal cardiac dyspnea; in 1, rheumatic heart disease; and in 1, congenital heart disease.

3. The frequency of angina pectoris and coronary occlusion and the infrequency of other types of heart disease may be due in part to the types of material studied, since chest leads were made more often when coronary disease was suspected.

4. In the absence of digitalis medication, we have not seen an upright T_4 in the electrocardiogram of any normal adult, when the anterior electrode was placed at the apex. Moreover, in our experience thus far, all adults with an upright T_4 have given us reason to suspect the presence of heart disease.

5. A T-wave in Lead IV which was isoelectric, or diphasic, with an upright component of 1 mm. or less, has been seen in patients with abnormal limb lead electrocardiograms in whom the presence of definite heart disease could not be proved.

6. Our observations suggest that, when an adult has an electrocardiogram which is normal in every respect, except for a definitely upright element in the T-wave in Lead IV, this should be considered an important finding, and the patient should be studied carefully for other evidence of heart disease, especially coronary disease. It is unsafe to disregard this sign.

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ISCHEMIC PAIN IN EXERCISING MUSCLES*

Its Nature and Implications

Albert H. Elliot, M.D., and Richard D. Evans, M.D.
Santa Barbara, Calif.

INTRODUCTION

WHILE the phenomenon of ischemic muscular pain lends itself readily to experimental observation by the use of a relatively simple technic, the number of metabolic factors which conceivably influence its behavior are numerous and are separable with difficulty so that the effect of each may be critically evaluated. From the possible methods of approach to this problem which might be adopted, we have selected those which aim to evaluate the rôle that the production and disposal of lactic acid may play.

The mere fact that pain occurs in exercising muscle deprived of blood has been known for many years, but it is only recently that this phenomenon has been subjected to careful experimental observation. The investigations of Sir Thomas Lewis and his associates[1] on this subject, which have in the main been corroborated by other observers, have laid the groundwork for our present conceptions which may profitably be summarized as follows:

1. Production of the pain substance is intimately concerned with the normal metabolic changes occurring during and after contraction of a skeletal muscle.

2. The pain substance is produced by a contracting muscle the circulation of which is free, but obstruction of the arterial flow, or decrease in the oxygen-carrying power of the blood, materially increases its speed of accumulation.

3. Under experimental conditions the phenomenon of muscular fatigue may be easily divorced from the occurrence of pain.

4. The pain substance is diffusible and under normal circumstances is rapidly washed away or destroyed. When the circulation is impeded, the substance which escapes from the muscle fiber may reach a concentration in the tissue spaces sufficient to stimulate sensory nerve endings. When circulation is reestablished, it is at once washed away and pain consequently ceases, but this does not necessarily mean that the metabolism of the muscle fiber has returned to normal.

The above facts seem well established. Further observations[2-6] suggest that:

1. Of the factors which are operative in dissipating the pain upon return of the circulation to an ischemic limb, the bringing of oxygen is

*From the Peripheral Vascular Clinic and the Cardiovascular Research Department of the Cottage Hospital, Santa Barbara.

of importance as well as is the mechanical dilution or washing out. If the oxygen content of the inrushing blood is materially decreased, the pain persists or dies out slowly.

2. The oxygen content of the blood is also of importance in determining the rate of formation of the pain substance in that, if it be sufficiently lowered, concentration of pain substance may rise to the point of stimulating sensory nerve endings even if the circulation to the limb remain unimpeded.

3. Certain observations suggest that the substance may be produced, although extremely slowly, in resting muscles deprived of blood. The evidence here is indirect and requires cautious interpretation.

4. Recent studies[7] have been offered as demonstrating that the pain substance can be trapped in resting muscles distant from its point of origin, but here again the evidence is not beyond criticism.

Insight into the chemical nature of the pain substance and its relation to the metabolic processes governing the expenditure of energy in the form of muscular contraction and recovery has up to now been entirely a matter for conjecture. It has been repeatedly suggested that the substance is probably an acid metabolite, and it is not surprising that lactic acid, known to be produced by contracting muscle and to be easily diffusible from it, has been suggested as the culprit. No studies aiming to establish definitely or to disprove such an hypothesis have to our knowledge as yet been undertaken.

Before presenting our observations it might be well to summarize the present knowledge[8] regarding the formation and fate of lactic acid in the body and to see if the laws governing lactic acid metabolism, in relation to muscular contraction, may be found consonant with or contrary to the known behavior of the pain substance. We do not here wish to enter into a discussion of muscular metabolism except so far as it bears upon the problem at hand. Lactic acid is derived from the breakdown of muscle glycogen. The rôle of this reaction in the immediate liberation of energy for muscular contraction is probably not important, but at the same time the reaction itself is an obligatory one. Under conditions of rest lactic acid production proceeds so slowly as not to exceed its rate of disposal, but upon muscular contraction its formation is at once increased many fold, and, if such contraction be repeated rapidly, the rate of formation quickly exceeds the possibilities for disposal within the muscle itself and lactate ion diffuses into the tissue spaces, to be picked up in some measure by the circulating blood. At a given moment, then, the concentration of lactic acid in the muscle will depend upon the ratio of rate of production to rate of disposal, and the concentration in the tissue spaces and blood will in addition be influenced by the rapidity of diffusion from the muscle cell and the adequacy of the circulation as determining its mechanical removal. Thus in severe sustained exercise the lactic acid content of

the blood is materially increased and may remain at a higher than normal level for an hour or longer. It is believed that in such circumstances lactate ion diffuses with facility both into the liver, where it is rebuilt into glycogen and, what is of great importance as regards the problem at hand, into resting muscles which have not participated in the preceding exercise.[9] Of the total amount of lactic acid formed during exercise, approximately one-fifth is later burned to carbon dioxide and water; the remainder, except for the escape of a small quantity through the kidneys, is reconverted into glycogen, primarily by the liver. These reactions occur during the recovery period following exercise. It should be emphasized that oxygen must be available before these changes can be accomplished. In contradistinction to the anaerobic release of energy making muscular contraction possible, the recovery phase is strictly contingent upon the presence of oxygen. It follows from this that any circumstance interfering either with the oxygen-carrying capacity of the blood or with sufficient irrigation by normal blood will lead to a local or general piling up of lactic acid in the tissues bearing the brunt of such disturbance.

To summarize: Lactic acid is rapidly produced by contracting muscle; it diffuses readily into the tissue spaces and blood stream; a large portion of it may be washed away from its point of origin if the circulation is adequate; its ultimate disposal by burning and by reconversion to glycogen demands available oxygen; if the blood concentration is sufficiently high, it may readily diffuse into resting muscles. Certain similarities between this behavior and that of the pain substance are at once apparent. The formation of both is an accumulative process when occurring during repeated muscular contraction. The concentration of each rises rapidly when circulation is impeded or when available oxygen is not present. Both diffuse readily from the muscle fiber into the tissue spaces. Available knowledge regarding the behavior of the pain substance does not allow us to draw this analogy further, but it may be said that to this point mutually exclusive characteristics of behavior are not encountered.

It is the purpose of this paper to present detailed observations which aim to test the hypothesis that lactic acid and the pain substance are identical. While a final answer cannot be given on the basis of our observations, it will be shown that this hypothesis adequately explains the experimental results obtained and that at least production and disposal of both lactic acid and pain substance are subject to similar metabolic laws.

METHODS

Our observations were conducted upon a group of four healthy young adults using a technic similar to that resorted to by other observers. With the blood supply occluded by a pressure of 200 mm. of mercury thrown upon the upper arm, a weight of 1,600 gm. was pulled through

a distance of 6.0 cm. by a submaximal grasp of the fingers at a rate of once a second. The time of onset of the pain, although found so variable as to prove of little ultimate significance, was noted in each instance, but the observation was terminated at the point where pain of the forearm became so severe as to preclude further muscular contraction. This end-point was found to be quite sharp in every instance and only rarely was it necessary to cease the determination because of fatigue, which was only encountered when the usual exercise tolerance was greatly exceeded. A gradual gain in ischemic exercise tolerance, which occurred over a period of months, is illustrated by Chart 1. The tolerance of the left arm was appreciably less than that of the right (all right-handed).

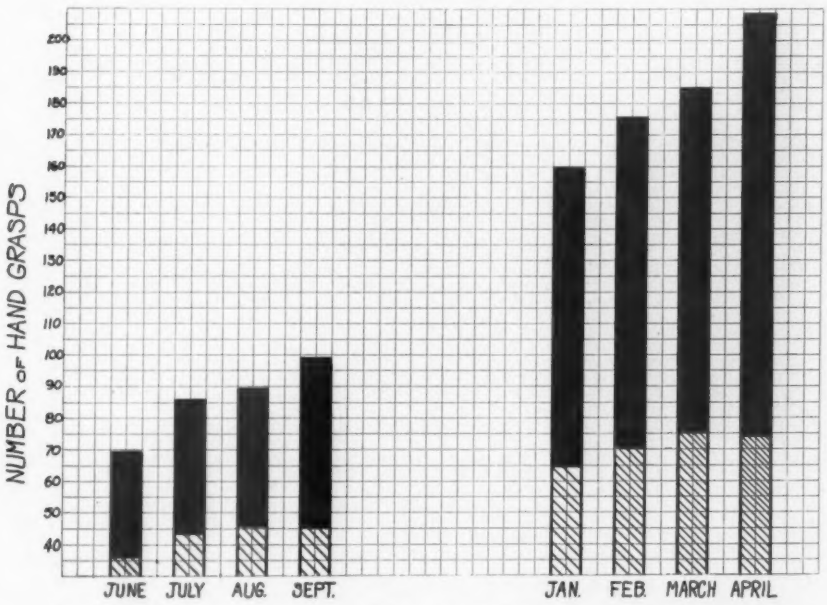

Chart 1.—Increase in forearm exercise tolerance over a period of months.

The level of lactic acid in the blood was determined on oxalated specimens taken from the veins of the resting forearm without stasis. The method of Mendel and Goldscheider was used. The percentage of error in our laboratory is approximately ±10.0. Blood sugar was determined on venous blood by the method of Schaffer and Hartmann.

RESULTS

As the first step it became necessary to establish control levels for the ischemic exercise tolerance of each individual. It was found that the exercise tolerance of one arm could be determined immediately following that of the other without its being appreciably influenced by this sequence. By studying the influence of varying the time intervals

between successive determinations conducted on the same arm, it was demonstrated that a rest period of fifteen minutes was sufficient to insure complete recovery of the exercised muscles. It was thus possible to measure the exercise tolerance of the same arm at fifteen-minute intervals over a period of two hours without exceeding a maximum variation of 15 contractions (7 per cent) above or below the value for the first determination and, in most observations, this variation was not greater than 5. As a further means of checking the possible influence of fatigue upon the frequently exercised muscles of one arm, the tolerance of the other arm was measured initially, after one hour, and at the conclusion of the second hour. These values were likewise found to vary little from one another. In most instances it was impossible to continue the observations longer than two hours because fatigue prohibited continuance of the exercise to the point of intolerable pain. However, this period of time proved sufficient for the purpose of these studies.

The consistency in behavior of the exercised forearm under conditions of bodily rest being thus established, the first problem investigated was that of the effect of nonischemic exercise of the leg muscles upon the pain tolerance of the forearm. The subject exercised upon a stationary bicycle peddling against a load as rapidly as possible until stopped by exhaustion. The arms were kept strictly at rest during this period, grasping of the handlebars being avoided. At the conclusion of the exercise the subject was seated in a chair and the exercise tolerance of the right forearm, checked at intervals by that of the left, was observed over a period of two hours in a manner identical with the control procedure. Occasionally an increase in the number of contractions possible was observed immediately at the close of the exercise period but an abrupt fall in tolerance occurred after an interval of fifteen minutes. In the succeeding determinations, intolerable pain developed at a progressively lower number of contractions until the thirtieth or forty-fifth minute, after which there was a gradual return of the forearm exercise tolerance toward the initial level which was usually reached in from 75 to 105 minutes. In Chart 2 the results of such an experiment are indicated in terms of number of contractions below the control level. The shape of this curve, which is characteristic of that encountered in numerous experiments of this kind, is strikingly different from the control curve also charted. It was further found that the decrease in exercise tolerance of the forearm resulting from exercise of the legs was roughly proportional to the intensity and duration of the latter. These results could be attributed either to changes in circulation through the resting forearm consequent upon acceleration of the circulation from leg exercise, or to an escape into the blood of a substance or substances formed in the exercising leg muscles which then diffused into the tissues of the forearm in sufficient quantity to augment the effect of the pain

substance produced by the ischemic forearm muscles themselves. The first hypothesis is unlikely because the effects observed persisted for some time after the pulse acceleration consequent upon the leg exercise had subsided.

The blood lactic acid values determined upon blood taken from the unexercised forearm at fifteen-minute intervals throughout the course of the experiment are likewise expressed on the chart. The curve is similar to those published by Hill, Long, and Lupton.[8] There is a precipitous rise immediately after the exercise, followed by a slow downward slope until the initial level is reached at the ninetieth minute. The similarity in shape between this curve and that of the exercise tolerance of the forearm is striking.

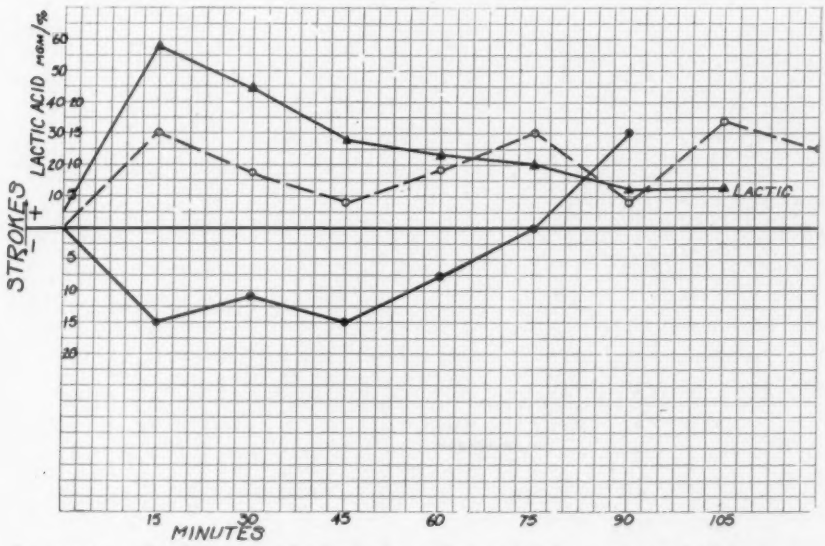

Chart 2.—Effect of vigorous leg exercise upon forearm exercise tolerance.

The next question to be studied was: Is the substance which escapes from exercising muscles with free circulation similar to, or identical with, the pain substance produced during ischemic exercise? As an approach to this problem, after numerous trials, the following experimental procedure was adopted: After determining the exercise tolerance of both forearms during bodily rest, the subject lay supine upon a bed with the legs elevated by two pillows. The circulation of each leg was then occluded above the knee, and the feet were forcefully extended and flexed once a second to the point of intolerable pain when the circulation was immediately reestablished. This procedure was repeated from three to six times with intervening rest periods of three minutes. The number of flexor-extensor movements of the feet possible under these conditions was found to decrease with each bout of exercise,

falling from an initial level of 70 to 80 movements to from 40 to 60. Parenthetically, it might be observed that an exercising nonischemic leg, under these conditions, will likewise become painful after a minute or two but that the exercise can be continued to the point of fatigue, pain increasing but slowly.

At the conclusion of the foot exercises the subject was seated in a chair. The exercise tolerance of the forearms was determined in a manner identical with that of the preceding experiment. A sample protocol is illustrated by Chart 3. The results were consistent and striking in all experiments. Here again a progressive loss in tolerance occurred which was far in excess of the variations encountered during the control determinations and which persisted over a period of from

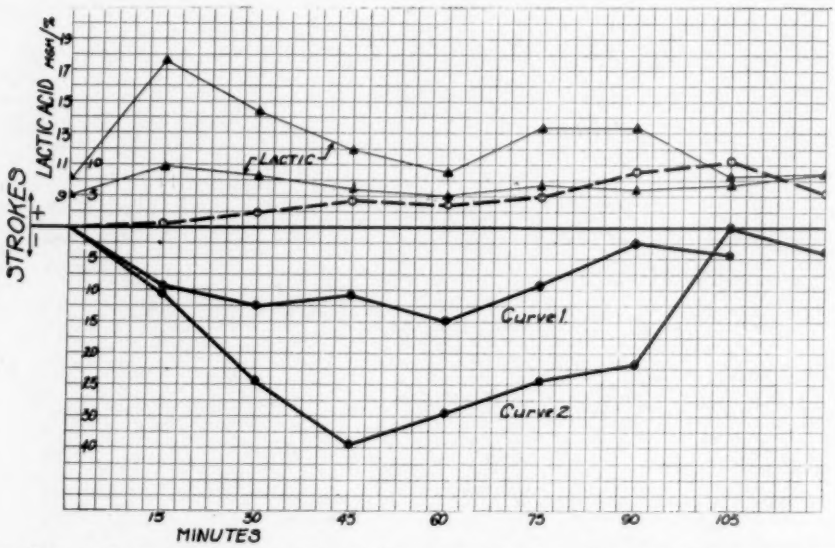

Chart 3.—Effect of release of pain substance from the legs upon the forearm exercise tolerance. *Curve 1*, after 3 releases. *Curve 2*, after 6 releases.

90 to 120 minutes. As illustrated by curves *1* and *2* (Chart 3), it was further found that the effect upon the muscles of the forearm was influenced by the number of times that the pain was built up in the legs. The lower curve shows the effect from six exercise cycles; the upper, that from three. These experiments demonstrate conclusively that pain substance built up in one group of ischemic exercising muscles escapes into the blood stream and circulates there for an appreciable length of time, which allows of its being trapped in other portions of the body where the effect of its presence may be unmistakably recognized. Is this effect traceable to an increase in the concentration of lactic acid in the blood? Lactic acid determinations conducted throughout the course of such experiments have shown a small but quite consistent elevation of the level in venous blood. Direct sampling of arterial

blood, which would allow a more satisfactory estimate of the concentration of lactic acid being brought to the forearm muscles, was not practical, but in one experiment samples of blood were taken from a forearm which was constantly immersed in warm water. The concentration in these samples, which should approximate closely the concentration present in the arterial blood itself, was slightly higher than in those of venous blood taken from the cool forearm.

It will be noted that the concentration of venous lactic acid returns to the initial level some minutes before the forearm exercise tolerance has reached the control value. The significance of this observation will be commented upon later.

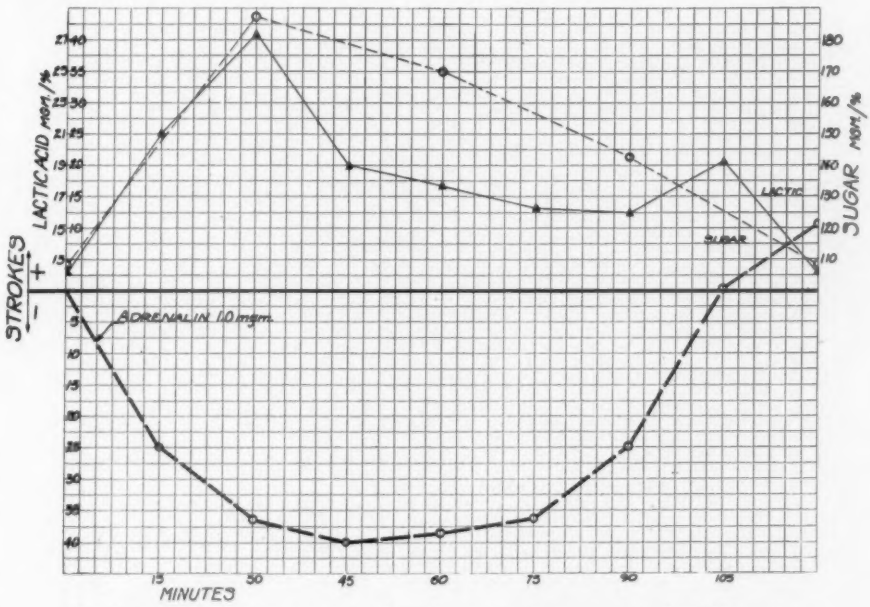

Chart 4.—Effect of 1 mg. of adrenalin upon forearm exercise tolerance.

The next group of observations was concerned with a study of the effect of increased blood lactic acid concentration, brought about by other means than exercise, upon the exercised forearm. In Chart 4 the effect of the intramuscular injection of 1.0 mg. of epinephrine upon the levels of sugar and lactic acid in venous blood, as correlated with the forearm exercise tolerance, is illustrated. It will be recalled[10, 11] that adrenalin exerts a profound influence upon the carbohydrate metabolism of muscle. Its primary effects are to accelerate the breakdown of muscle glycogen into lactic acid and probably to inhibit the utilization of sugar brought to the muscle. In the blood these influences are reflected by lactic acidemia and, in part, by hyperglycemia. As Chart 4 shows, the effect persists for about two hours, and the curve for decrease in forearm exercise tolerance was, in our experiments, of the same pattern as,

but in opposite direction to, those illustrating the concomitant changes in the blood. Since, however, lactic acidemia from epinephrine is accompanied by hyperglycemia, it was necessary to determine the influence of the latter upon the exercised forearm muscles. We sought to determine if hyperglycemia influenced either the speed of formation of pain substance in the ischemic forearm muscles themselves, or the fate of the pain substance released from the legs. The fasting subject, immediately after the tolerance for ischemic exercise of each forearm had been ascertained, consumed 100 gm. of glucose. Changes in exercise tolerance of the forearm were then observed at fifteen-minute intervals in the usual manner. In several such experiments a surprising rise in the number of contractions possible was found during the latter part of the

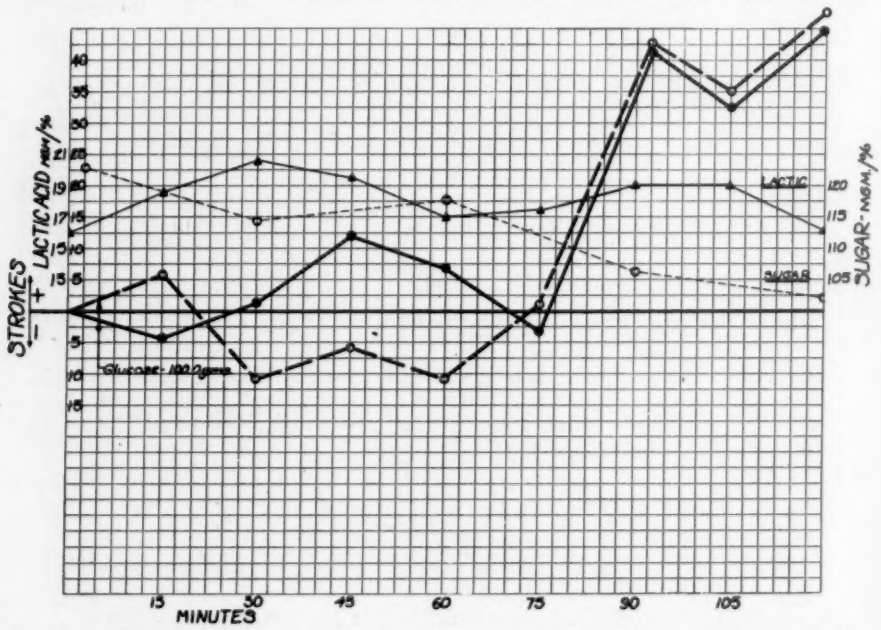

Chart 5.—Effect of 100 gm. of glucose upon forearm exercise tolerance with and without release of pain substance from the legs.

two-hour period, the subject often being forced to stop the exercise from fatigue rather than from pain. When a study of the concentration of the pain substance in the blood after its release from the legs was attempted, following glucose administration, an increased concentration could not be demonstrated by trapping in the forearm. The usual decrease in forearm tolerance was entirely lacking. The curve coincided closely with that obtained in the first or control glucose experiment. These results are illustrated in Chart 5, including the venous blood sugar values, which in this subject showed no rise. The curve for blood lactic acid during this experiment is similar to those obtained when glucose is not administered. Also, intolerable pain developed in the legs just as quickly. Evidently the effect of glucose upon the rapidity of production of pain substance is not apparent until approximately

75 or more minutes have elapsed from the time of its ingestion. The leg exercises were initiated immediately after the ingestion of the glucose, and during the first half hour (the time necessary to complete six cycles of leg exercise) no increase in tolerance of the forearms was noted in the control experiment.

That the presence of pain substance in the blood following release from the legs is no longer recognizable from its effect upon forearm exercise tolerance is difficult to explain. Either the metabolism of the muscles is significantly changed by glucose ingestion, or else, which is more unlikely, hyperglycemia in some manner inhibits diffusion of pain substance from blood to tissues. These results merit further investigation.

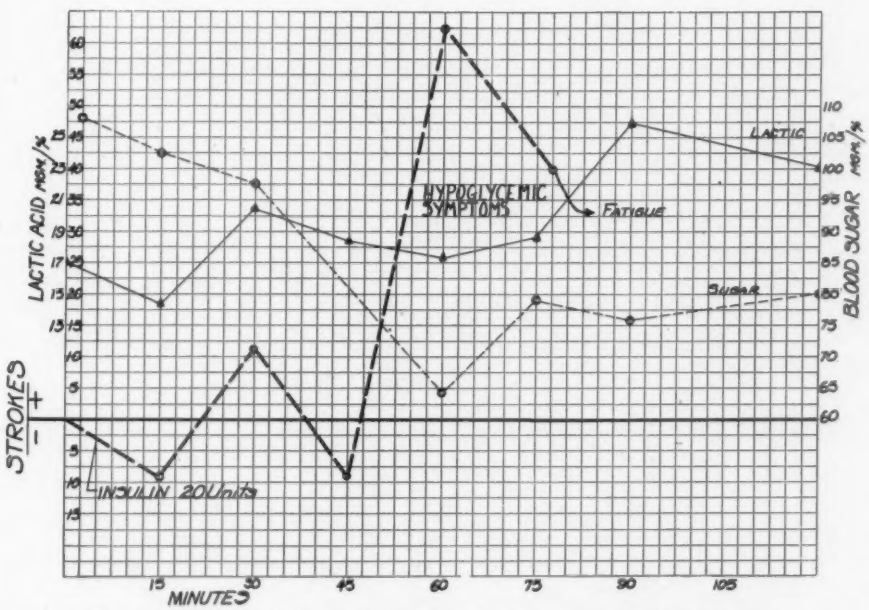

Chart 6.—Effect of hypoglycemia upon the forearm exercise tolerance.

The effect of hypoglycemia upon the formation and fate of the pain substance has been observed in a few instances. The experimental procedure was identical with that above except that the intramuscular administration of 20 units of insulin was substituted for ingestion of glucose. In two such experiments consistent effects upon forearm exercise tolerance, with or without release of pain substance from the legs, could not be demonstrated. However, the subject did not experience hypoglycemic symptoms. In a third experiment upon another subject the blood sugar fell from 106 to 64 mg. per cent within one hour. This fall was accompanied by rather pronounced symptoms, but exercise of the forearm could be continued well beyond the point at which intolerable pain became evident in the control determination. Blood lactic acid was not elevated during this time. Determination of exercise tol-

erance beyond the sixty-minute interval was not satisfactory because of muscular fatigue, but the onset of pain appeared to be delayed. At the conclusion of two hours following insulin, there was an appreciable lactic acidemia which might be the result of compensatory outpouring of adrenalin. This course of events (Chart 6), difficult of interpretation as regards specific effects upon the pain substance, should be corroborated by further study.

The last group of experiments is concerned with the effect upon ischemic pain of the administration of sodium lactate by the oral and intravenous routes. The sodium lactate for oral ingestion was prepared by adding sodium bicarbonate to a weighed amount of acid in sufficient quantity to bring the pH to approximately 6.0. The mixture was then

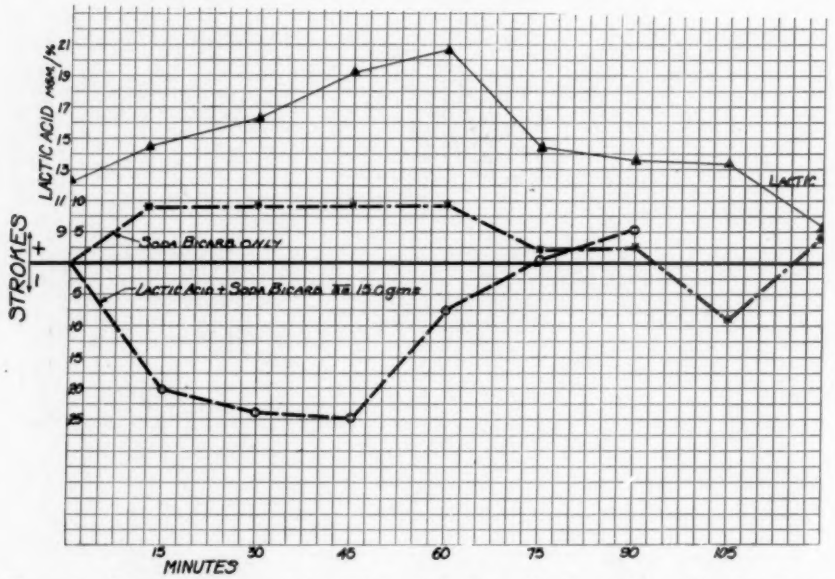

Chart 7.—Effect of the oral ingestion of lactic acid plus sodium bicarbonate and of sodium bicarbonate only upon forearm exercise tolerance.

diluted to a volume of 200 c.c. and taken when fasting. Forearm exercise tolerance was measured before and after this in the usual manner. The dosage of sodium lactate varied from 10 to 20 gm. In some experiments exercise tolerance was not influenced, and the subject had a bowel evacuation within a comparatively short period following its ingestion. In one such experiment it was found that the blood lactic level was not elevated, indicating lack of absorption from the intestinal tract. In another experiment there was an appreciable decrease in exercise tolerance, which persisted for over an hour, but no change in the level of venous lactic acid. In the remaining experiments, a sample of which is given in Chart 7, there was both a drop in the number of hand grasps possible and a concomitant lactic acidemia. In a control experiment following the ingestion of an amount of sodium

bicarbonate equal to that used for the neutralization of the lactic acid preparation, namely 15.0 gm., no effect upon the muscles of the forearm was evident.

In a final experiment, 60 c.c. of molar sodium lactate (approximate content 6.0 gm.) diluted to a volume of 180 c.c. was administered intravenously. As illustrated in Chart 8, concentration of blood lactic acid rose from 25 to 38 mg. per cent during the injection. At its conclusion the level had fallen to 32.9 mg. It continued to fall during the next thirty minutes until a low concentration of 20 mg. per cent was reached. The immediate decrease in forearm exercise tolerance during the injection was striking. The exercise curve continued downward, reaching its lowest point simultaneously with that of the blood lactic acid. After

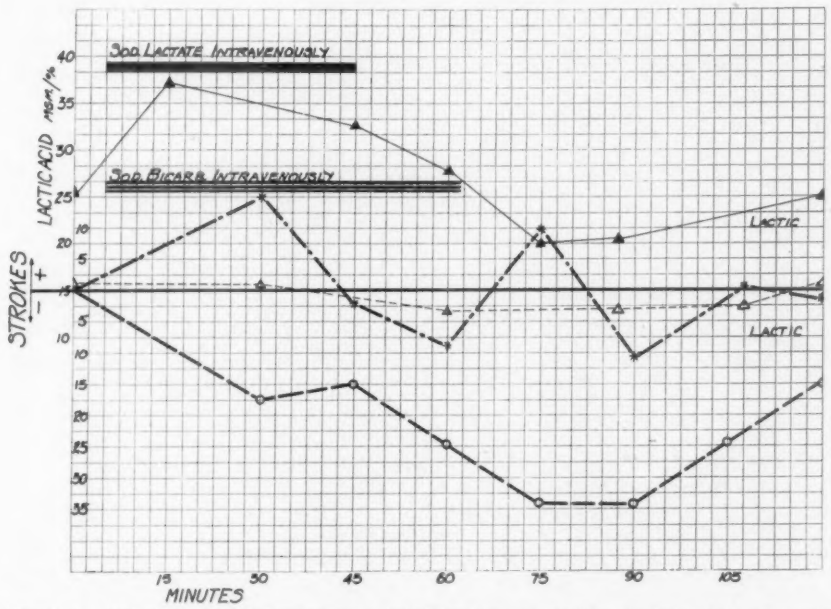

Chart 8.—Effect of the intravenous administration of sodium lactate (60 c.c. molar solution) and of sodium bicarbonate (6.0 gm.) upon forearm exercise tolerance.

this, it turned abruptly upward but did not reach the control level within two hours. At this time, the observations had to be terminated because of fatigue of the forearm, the pain end-point proving unattainable. It was likewise necessary to control this experiment by the giving of an equivalent amount of sodium bicarbonate in a solution of equal hypertonicity. That neither a significant change in exercise tolerance nor in blood lactic acid content resulted is shown in Chart 8.

DISCUSSION

Before attempting to analyse the observations herein reported as regards their bearing upon what we might term the lactic acid hypothesis, attention should be called to certain factors which might easily obscure their significance. In the first place, all blood analyses were done on

venous samples, which may not give a true picture of the potentiality for the diffusion of lactate ion from blood to muscle and tissue spaces. In other words, the level of lactate ion in blood returning from resting muscle may be normal, and yet its concentration in and about the muscle actually increased as the result of diffusion from arterial blood containing a higher than normal content. This might serve to explain in part the fact that in many experiments the exercise tolerance of the forearm did not return to the initial level until some minutes after the blood was found to be carrying a low content of lactic acid. It is possible that the concentration of lactate ion in the muscle may remain increased for an appreciable time after it is no longer augmented by diffusion from the arterial blood stream. Another fact of possible significance is that the concentration of lactate ion in the muscle would, under rest, reach an equilibrium with that of the plasma, which is 33 per cent greater than the concentration in whole blood.[8] Our observations were conducted at fifteen-minute intervals, and it would seem that if the blood lactic acid content were changing rapidly, the rest periods were hardly ample enough to insure that a state of equilibrium between blood and tissues had actually occurred at the time of the observation. Assuming, then, that lactic acid accumulation in and about sensory nerve endings is in fact immediately responsible for the occurrence of ischemic pain, it would appear from the above considerations that analyses of venous blood would at best reflect only indirectly the magnitude of such accumulation and therefore a strict parallelism between exercise tolerance and blood lactic acid content could hardly be expected in all experiments. An analysis of our observations from this point of view at once discloses some significant facts. Lactic acidemia, as brought about by exercise, epinephrine, or the introduction of sodium lactate into the body, was regularly accompanied by an earlier appearance of ischemic pain in the muscles of the forearm. In most experiments this effect outlasted the rise in blood lactic acid content, but in no instance did exercise tolerance return to normal in the face of continuing lactic acidemia. The converse of this was not always true, namely, decreased forearm exercise tolerance often occurred without rise in blood lactic acid but, for reasons previously stated, the inference must not necessarily be drawn that the concentration of lactate ion about the nerve endings was likewise low. We do not regard this evidence, therefore, as entirely unharmonious with the provisions of the hypothesis. It is further apparent that the degree of hastening of the pain end-point was not in proportion to the intensity of the lactic acidemia. The maximum decrease in the possible number of hand grasps observed in our experiments was 40 (21 per cent), and this occasionally occurred at a time when the concentration of lactic acid in the blood had returned to normal. This lack of parallelism between the two phenomena can be explained by assuming that the tissues of the forearm are capable of taking up only a maximum fixed amount of lactate ion by diffusion from arterial blood and that the speed of its

accumulation might vary with the content of lactic acid in the arterial blood coming in contact with them. During the initial stages of lactic acidemia, the rate of diffusion of lactate ion from blood to tissues should be rapid, but as the tissue concentration rises, the diffusion rate in this direction might proportionately decrease until the blood lactate level becomes low, at which time it is reasonable to suppose that the direction of diffusion reverses itself, lactate ion now passing from tissues to blood. This conception adequately explains the typical course of events seen in most of our experiments; namely, a rapid drop in exercise tolerance during the first fifteen or thirty minutes of induced lactic acidemia when the diffusion rate is rapid, a flattening out of the curve as diffusion from blood to tissue becomes slow, a gradual recovery by reversal of direction of diffusion occurring after the concentration in the blood has fallen to normal.

Some of our experimental observations, however, are not in strict agreement with the hypothesis that lactic acid is the sole substance responsible for ischemic muscular pain. In some of the experiments dealing with trapping of the pain substance in the forearm after its release from the legs, no rise in lactic acid content of the blood was encountered, whereas the decrease in forearm exercise tolerance was consistent and unmistakable. Likewise, its magnitude was quite comparable with that occurring from induced lactic acidemia. This may well indicate that another substance or substances may be capable of producing ischemic pain. In one such experiment the level of inorganic sulphate of the blood was followed, but no appreciable change occurred. Anrep and von Sallfeld[12] have recently shown that there is released from contracting muscle a stable vasodilator substance which they identify, on the basis of biologic assay, as histamine. We carefully sought for evidences in our experiments of histamine effect upon the general circulation following repeated release of pain substance from the legs. No fall in blood pressure or flushing was ever observed, nor was the electrocardiogram altered. In many subjects, however, a slight fall in pulse rate, varying from 6 to 10 beats, occurred in from eight to twelve minutes after the sixth release. This phenomenon is worthy of further study, particularly since a similar occurrence has recently been noted in cardiac patients following work on the ergometer.[13]

Another series of observations which are not strictly in accord with the lactic acid hypothesis are those dealing with the effect of glucose upon the formation and disposal of the pain substance. It will be recalled that the exercise tolerance of the forearm was materially increased and the trapping of pain substance could not be accomplished. In one such experiment there was a slight rise in the concentration of blood lactic acid, but no alteration of forearm exercise tolerance was demonstrated.

CONCLUSIONS

Our conclusions from the evidence herein presented are:

1. The substance or substances responsible for pain in exercising

ischemic muscles are relatively stable, may be present in the blood stream for an appreciable period following their release from such muscles, and may diffuse into tissues distant from their point of origin.

2. Such substance or substances are produced likewise in nonischemic exercising muscles, and their concentration in the blood stream following vigorous exercise is materially increased for an hour or longer.

3. Increase of lactate ion in the muscles of the forearm, brought about by whatever means, uniformly enhances the action of the pain substance produced by these same muscles.

4. Probably an increased concentration of lactate ion about the sensory nerve endings can, per se, produce pain, such increase not necessarily exceeding metabolic limits.

5. It is possible that lactate ion is solely responsible for the production of ischemic pain, but release of other substances, which are beyond doubt subject to similar metabolic laws, may play a rôle, and these should be investigated.

We wish to thank the volunteers who subjected themselves to these experiments and Miss L. Jemtegaard for technical assistance.

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CREATINE CHANGES IN HEART MUSCLE UNDER VARIOUS CLINICAL CONDITIONS*†

GEORGE HERRMANN, M.D., GEORGE DECHERD, M.D., AND TOM OLIVER, M.D.
GALVESTON, TEXAS

THE establishment of a satisfactory explanation of the physiology of skeletal muscle contraction on a chemical basis involving phosphocreatine has revived interest in the chemistry of heart muscle under various clinical and experimental conditions. The new approach seems to offer some promise of elucidation of such intricate problems as the finite basis of myocardial weakness, of cardiac hypertrophy, and perhaps even of pharmacodynamic action. A more fundamental explanation of heart failure has long been demanded by clinicians, impressed by the frequent absence of adequate gross and microscopic findings to explain the clinically observed complete functional insufficiency of the cardiac musculature.[1] That something more than morphological changes must be sought out has been frequently indicated, and that biochemical changes may play an important rôle has been suggested.

BIOCHEMICAL BACKGROUND

Constabel[2] in 1921, following the earlier suggestion of Pekelhering[3] that increased muscle tonus was associated with higher creatine content, found that the creatine content of atonic, dilated or damaged human hearts was usually low. These observations were apparently lost for thirteen years. During these intervening years, however, the great mass of experimental work on the physiological chemistry of skeletal muscle contraction has been carried out in Germany, in England, and in the United States. Since 1922 significant contributions to our knowledge of this subject of muscle physiology have been published from Embden's laboratory. In one of the early papers Embden and Lawaczech[4] presented observations of reactions which demonstrated the importance of organic phosphates in muscle physiology. The interpretation, that the observed increase in inorganic phosphates as well as the formation of lactic acid during muscular contraction came from a hexosephosphate, lactacidogen, was apparently in error. Lohmann[5] later (1928) showed that, by the method used by Embden, the orthophosphate yield came mostly from the splitting of pyrophosphate and only in small part from the lactacidogen, and

*From the Department of Medicine and Pathology of the University of Texas.

†Read at the meeting of the American Heart Association held at Kansas City, Mo., on May 12, 1936. By an unfortunate error the discussion of this paper at that time was omitted from the Transactions of that meeting published in the October issue of this Journal.

that nucleotide pyrophosphate was an important compound in muscle metabolism. Lohmann noted distinct decrease in pyrophosphate on contraction and also noted that the pyrophosphate was linked to adenylic acid. The splitting off of ammonia (NH_3) in muscle contraction was found by Embden and Zimmermann[6] and by Parnas and Mozolowski[7] to come from adenylic acid. Embden correlated the endurance of muscle for prolonged contraction with its phospholipid content.

Lundsgaard's halogen acetic acid experiments[8] proved that muscle work is possible, and consequently that the chemical processes of contraction may occur, without the formation of lactic acid. This relegated lactic acid formation to a secondary position and fitted in with the observations of Embden and his coworkers that the pH of the muscle changed to the alkaline side, not to the acid side, at the instant of contraction.

Fiske and Subbarow,[9] however, clarified the whole matter when they discovered that creatine phosphoric acid as a secondary potassium salt, phosphocreatine, was the active principle that made up part of what had previously been determined as orthophosphate. Eggleton and Eggleton[10] simultaneously identified the active substance as "phosphagen" an unstable form of organic hexosephosphate, a phosphoric ester of glycogen, or a precurser of both lactacidogen and lactic acid. Later these authors acknowledged "phosphagen" to be creatine phosphoric acid or phosphocreatine. Nevertheless, glycogen-lactic acid metabolism is essential, supplying as it does the energy for phosphocreatine resynthesis, while the intermediary products as hexosephosphate act as buffers.

Embden and Lehnartz[11] had emphasized the reversible phosphate breakdown and rebuilding in recovery, with decrease of the synthesis in fatigued muscle. Fiske and Subbarow[9] determined that the phosphocreatine-glycogen ratio in skeletal muscle remained fairly constant; both decreasing equally under aerobic conditions, while in anaerobiosis the phosphocreatine disappears more rapidly than the glycogen and the ratio falls. Phosphocreatine was found to be relatively stable in an alkaline medium, yet it hydrolyzed with increasing velocity as the pH rose. A lactic acid acidosis results in a loss of creatine and of potassium from the muscle cells. Creatine, phosphates and potassium were thus established, along with glycogen and lactic acid, in skeletal muscle physiology. With these facts before them it was logical for investigators to apply the same methods to the study of heart muscle physiology.

Vollmer[12] found phosphocreatine constituting from 75 to 80 per cent of the total creatine content of the resting ventricular muscle of the slow beating thin-walled turtle heart. He noted that the phosphocreatine dropped to from 20 to 25 per cent of the total creatine after

contraction. Pollack, Flack, Essex and Bollman[13] have made similar, but technically much more difficult, studies of phosphocreatine in dogs' hearts from the Starling heart-lung preparations. The failure of these investigators to confirm Vollmer's findings may be due in large measure to the difficulties inherent in mammalian heart studies, namely, the inability to freeze the muscle in the desired phase of contraction.

HUMAN HEART MUSCLE CREATINE STUDIES

The experimental studies as to the creatine and phosphocreatine changes in cardiac muscular contraction seemed to indicate that processes similar to those of skeletal muscle physiology were at work. Renewed interest was aroused by these reports in the problems of human heart function. Constabel's findings were recalled and extended by Vollmer and others and various other chemical studies were undertaken. Wilkens and Cullen[14] noted a decrease in total phosphorus and potassium in the heart muscle from patients who had died in congestive failure. Scott,[15] with material supplied him by one of us, confirmed the potassium loss. Seecof, Linegar and Myers[16] followed up Constabel's and Vollmer's studies of the creatine content and reported the creatine values for the various parts of 102 human hearts. They found the left ventricular muscle to contain uniformly more creatine than the right, with a mean of 243 mg. per cent for the left and 188 mg. per cent for the right, averages of 211 and 148 mg. per cent, respectively, and ranges of from 116 to 369 as against 93 to 283 mg. per cent. Vollmer had reported the left ventricle to contain 221 mg. per cent and the right 173 mg. per cent—a 20 per cent difference—whereas Constabel had elicited only a 10 per cent difference.

Cowan[17] has supplied corroborative evidence of Constabel's early contention that lowered total myocardial creatine values were found in hearts that had been seriously damaged. In 11 of 17 hearts from patients who had died in congestive failure, he recorded total creatine values of from 92 to 152 mg. per cent. These figures are low as compared with those found in "normal" hearts (from patients who had died of other causes) which showed mean values of 202 mg. per cent $\pm$ 37.

Under our direction in this laboratory W. O. Brown, Jr., analyzed, as our first series,[18] the left ventricular muscle from 50 adults, kindly supplied us from autopsies by Dr. Tom Oliver, Dr. Jarrett Williams and Dr. Sion Holley, of the staff of the Department of Pathology. Thirteen of the 50 hearts were from patients with congestive failure and in these the creatine values ranged from 85 to 132 and averaged 111 mg. per cent, whereas in 10 hearts from patients with syphilitic aortic disease, the values ranged from 110 to 137, and averaged 123

mg. per cent. In a miscellaneous group without gross heart disease the creatine values ranged from 123 to 205, with an average of 150 mg. per cent.

PRESENT STUDIES

A second series of 105 human hearts, in which the left ventricular muscle has been analyzed in our laboratory,* furnishes the basis for this paper. The creatine values in this second and larger group of hearts correspond quite closely to the previously reported findings, but they will be set down in detail as a matter of record.

TABLE I

CREATINE CONTENT OF NORMAL HUMAN HEARTS
(SECOND SERIES)

AGE	SEX	RACE	HT. WT.	CR. (MG. %)	SOLIDS %	DR. CR. (MG. %)
			A. Death From Trauma			
31	M	W	310	145	21.8	666
18	M	W	275	176	20.4	863
50	M	W	340	169	20.1	840
16	M	B	180	196	20.0	980
55	M	W	110	173	20.6	838
58	M	W	375	183	20.9	875
38	M	B	300	180	21.2	847
29	M	W	290	210	20.0	1050
45	M	B	350	187	20.7	900
48	F	W	210	212	21.6	982
57	M	W	390	185	20.3	912
				183	20.7	887
				±17	±0.62	±79
			B. Death From Infectious Disease			
69	M	W	350	175	20.7	845
43	M	W	300	156	18.6	838
45	M	W	200	171	20.0	855
80	F	W	300	155	18.6	832
48	M	W	440	172	20.1	858
13	F	B	125	209	21.9	955
49	M	W	365	250	22.6	1105
43	F	W	220	168	19.3	872
26	M	W	285	163	19.8	823
40	M	W	300	187	20.2	930
36	M	W	340	176	20.0	878
9	F	W	115	159	20.1	790
50	M	W	390	184	20.2	910
43	M	B	330	180	21.1	855
30	F	B	200	191	20.6	910
72	M	W	400	185	20.6	900
36	F	B	175	145	19.3	752
38	M	B	250	151	20.6	733
35	F	W	320	150	23.4	641
25	F	W	265	149	20.4	730
21	F	W	185	155	18.1	858
24	F	B	250	161	18.7	864
				172	20.1	858
				±15.4	±0.96	±70
				175	20.3	868
				±20.7	±0.87	±76

*These analyses were made by Peter S. Erhard.

The results were tabulated according to the clinical and post-mortem data under the headings: 1, apparently normal hearts; 2, grossly abnormal hearts that had not shown failure; 3, hearts from patients dying of congestive cardiac failure; and 4, infarcted hearts from patients with coronary thrombosis.

Group 1.—There were 34 hearts which were apparently normal, the analyses of the left ventricular muscle of which showed an average

TABLE II

HEART DISEASE WITHOUT FAILURE

AGE	SEX	RACE	HT. WT.	CR. (MG. %)	SOLIDS %	DR. CR. (MG. %)
			A. With Hypertension			
72	M	B	400	221	21.6	1022
68	M	B	510	204	20.8	989
38	M	B	510	158	19.4	814
68	M	W	540	199	20.1	992
48	M	B	645	198	21.1	937
45	M	B	410	207	19.5	1063
				198	20.4	970
			B. With Coronary Sclerosis			
73	M	W	335	144	19.7	731
60	M	W	325	148	21.4	690
53	M	W	295	176	19.4	907
67	M	W	250	119	19.2	622
89	M	W	325	137	19.7	695
60	M	W	475	143	18.8	764
45	M	W	350	187	20.8	900
72	M	W	320	175	20.5	853
45	M	B	260	159	19.2	831
70	M	W	230	175	21.5	815
64	M	W	285	162	20.2	800
				157	20.0	783
			C. With Rheumatic Aortic and Mitral Disease			
41	M	B	450	210	19.9	1058
				173	20.1	860
			SEVERE ANEMIAS			
43	M	B	290	144	17.2	837
55	M	W	425	137	19.7	735
67	M	W	250	119	19.2	622
29	M	W	290	210	20.0	1050
72	F	W	320	175	20.5	853
				157	19.3	819
			GLOMERULONEPHRITIS WITH UREMIA			
43	F	W	435	150	19.6	785
49	F	B	400	169	20.0	845
48	M	B	400	146	20.7	706
40	F	B	280	165	21.8	756
45	M	B	260	159	19.2	831
39	F	B	420	168	22.0	763
				159	20.3	781

total creatine content of 175 mg. per cent ± 20.7 total solids of 20.3 per cent ± 0.877, and dried muscle values of 868 mg. per cent ± 70 (Table I).

Group 2.—A series of 30 hearts from patients with heart disease, but without heart failure, presented creatine values that averaged about the same as those of the normal hearts, namely, 173 mg. per cent, 20.1 per cent, and 860 mg. per cent. Of these, one from a patient with rheumatic aortic regurgitation and mitral disease was found to contain 210 mg. per cent creatine, 19.9 per cent solids, and 105.8 mg. per cent in dried left ventricular muscle.

Six hearts from patients with hypertension, but not in failure, showed an average of 198 mg. per cent ± 15.6 of creatine, 20.4 per cent of solids, and 970 mg. per cent ± 79 of dried muscle; while 11 with coronary sclerosis alone averaged 157 mg. per cent creatine, 20 per cent solids, and 783 mg. per cent dried muscle.

In the left ventricular muscle of hearts from six patients who died in uremia with glomerulonephritis the creatine value averaged 159 mg. per cent, the solids, 20.3 per cent and the dried muscle, 781 mg. per cent; the values in five cases of severe anemia averaged 157 mg. per cent in creatine, 19.3 per cent in solids and 819 mg. per cent in dried muscle (Table II).

Group 3.—Of particular interest to us is the small series of four hearts from patients who died following acute coronary thrombosis. In these the heart muscle from the region of the infarct uniformly showed striking losses of creatine when compared with the uninfarcted myocardium. In most instances the relation was about 2 to 1. In these hearts the creatine level in the uninfarcted muscle was also

TABLE III

A. CORONARY OCCLUSION

HT. WT.	CREATINE (MG. %)		SOLIDS (%)		DRIED (MG. %)	
	GOOD	INFARCTED	GOOD	INFARCTED	GOOD	INFARCTED
610	122	41	23.45	18.0	520	228
350	104	61	21.95	15.05	497	405
800	100	52	19.7	18.2	558	318
900	151	31	19.15	17.25	788	180

B. SEVERE PROLONGED AND COMPLICATED INFECTIOUS DISEASES

HT. WT.	CREATINE (MG. %)	SOLIDS (%)	DRIED (MG. %)
340	101	18.2	556
375	131	22.0	596
385	111	23.0	482
375	129	19.0	681
250	110	19.1	577
300	101	22.6	448
350	136	21.1	645
300	143	22.4	641
340	139	19.6	710
210	114	18.4	623
	121	20.5	596

reduced to about the same concentrations found in the hearts of patients with congestive failure (Table III, A).

Ten hearts from patients with prolonged and complicated infectious diseases, with microscopic evidence only of myocardial damage, presented similarly low creatine figures, averaging 119 mg. per cent, with 20.8 per cent solids and 671 mg. per cent in terms of dried weight (Table III, B).

Group 4.—Thirty-two hearts from patients who had died in congestive failure were found upon analysis to contain about 30 per cent less creatine than normal with the following values for the left ventricular myocardium: creatine, 122 mg. per cent ± 20.8; solids, 20.3 ± 1.2 per cent; and dried weight, 605 mg. per cent ± 100 (Table IV).

These values corroborate our previous reports and those of others except for the ten low values found in infectious diseases of a chronic and complicated type, as shown in Table III, B.

TABLE IV

CREATINE CONTENT OF HEARTS FROM PATIENTS DEAD OF CONGESTIVE FAILURE (SECOND SERIES)

AGE	SEX	RACE	ETIOLOGY	HT. WT.	FRESH (MG. %)	SOLIDS (%)	DRIED (MG. %)
58	M	W	Hypertension + C.O.*	550	130	21.10	617
45	M	B	Sclerosis	520	106	20.70	512
20	M	W	Hypertension	820	154	21.1	738
70	M	B	Coronary sclerosis	560	85	18.7	453
45	F	B	Hypertension	650	95	19.1	497
34	F	B	Syphilis	560	118	20.4	577
63	M	W	Sclerosis	440	140	19.3	723
50	M	B	Syphilis	540	120	20.0	600
39	F	B	Hypertension	475	100	18.6	537
50	M	W	Syphilis	850	135	20.05	673
55	M	W	Hypertension	600	112	19.9	563
68	M	W	Sclerosis	375	130	21.0	618
73	M	B	Sclerosis	345	125	20.0	625
57	M	W	Hypertension + C.O.	610	103	18.3	562
50	F	B	Hypertension	610	132	20.1	657
54	M	W	Syphilis + Anemia	425	137	19.7	696
59	M	W	Hypertension + C.O.	700	122	23.4	520
76	M	W	Hypertension	580	109	20.5	532
30	M	B	Sclerosis + C.O.	375	145	20.5	705
50	M	B	Hypertension	540	165	21.0	785
67	M	B	Hypertension	650	109	19.1	572
41	M	W	Hypertension	460	133	20.5	649
60	M	W	Sclerosis + C.O.	350	104	21.9	497
69	M	B	Hypertension + C.O.	800	110	19.7	558
50	M	B	Syphilis + C.O.	900	151	19.1	788
75	F	B	Hypertension	500	144	20.8	690
65	M	B	Hypertension	495	138	20.7	667
49	M	B	Syphilis	650	112	23.4	478
56	M	B	Hypertension	600	100	21.7	457
70	F	W	Hypertension	430	130	21.7	598
32	M	B	Syphilis	400	91	17.8	511
65	M	B	Hypertension	340	139	19.6	710
			Averages		122 ±20.8	20.3 ±1.22	605 ±100

*C.O., coronary occlusion.

Cowan did not find low creatine values as the result of infectious diseases, but Constabel reported figures quite similar to ours. In fact, our normals are distinctly below those reported by Cowan, but again agree with Constabel's normal levels (Table V).

TABLE V

CREATINE CONTENT OF HUMAN HEARTS

NO.	CAUSE OF DEATH	FRESH (MG. %)	SOLIDS (%)	DRIED (MG. %)
11	Traumatic	183 ± 17.0	20.7 ± 0.62	887 ± 79
23	Infections	172 ± 15.4	20.1 ± 0.98	858 ± 70
34	Controls	175 ± 20.7	20.3 ± 0.87	868 ± 70
	Heart disease without failure			
1	Rheumatic, aortic, and mitral	210	19.9	1058
6	Hypertension	198 ± 15.6	20.4	970 ± 79
11	Coronary sclerosis	157	20.0	783
18	Total without failure	173	20.1	860
6	Glomerulonephritis with uremia	159	20.3	781
5	Severe anemia	157	19.3	819
32	Congestive heart failure	122 ± 20.8	20.3 ± 1.2	605 ± 100
10	Infections with microscopic myocardial change	121	20.5	596

CONCLUSIONS

The results of our studies, and those of others, convince us that low human myocardial creatine values are more or less constant accompaniments of congestive failure and must be among the significant chemical changes that are associated with myocardial damage and insufficiency. Particularly significant are the extremely low total creatine contents of the myocardium from the infarcted areas in cases of coronary thrombosis.

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THE EFFECT OF POTENTIAL VARIATIONS OF THE DISTANT ELECTRODE ON THE PRECORDIAL ELECTROCARDIOGRAM*

CHARLES E. KOSSMANN, M.D.
WITH THE TECHNICAL ASSISTANCE OF
BERTHA RADER, A.B.
NEW YORK, N. Y.

THE most important of the controllable factors that influence the form of the precordial electrocardiogram may be listed as (1) the location of the exploring† electrode, (2) the size of the exploring electrode, and (3) the potential of the indifferent† electrode. The effect of the first has already been adequately demonstrated by the extensive work of Wilson and his associates.[1-5] The second will be taken up in a later publication. It is the purpose of this article to emphasize the significance of the potential of the distant electrode in the determination of the form of the curve obtained when the exploring electrode is placed over the precordium.

Leads IV, V, and VI as described by Wood, Bellet, McMillan, and Wolferth[6] are suitable for an analysis of this type because they serve to bring out some very obvious, though apparently not very well known, relationships. In taking these leads, the right arm electrode is placed on the precordium in the vicinity of the apex, the left arm electrode on the back at a point just medial to, and below, the inferior angle of the left scapula, and the left leg electrode on the left leg. By pairing in succession, the precordium with the back, the precordium with the left leg, and the back with the left leg, Leads IV, V, and VI, respectively, are obtained. By joining each pair with a straight line it is easy to visualize a triangle laid out in the sagittal plane of the body to the left of the midline. Roughly, this triangle is equilateral, but whether it be regarded so or not, it can easily be shown that Lead V equals Lead IV plus Lead VI. The simple principle upon which this rule depends is the same as that upon which Einthoven's law that Lead II equals Lead I plus Lead III also depends. This principle, recently discussed by Wilson, Macleod and Barker,[7] is that the difference in potential between two points is the

*From the Department of Medicine and Therapeutics, New York University College of Medicine, and the Third (N. Y. U.) Medical Division of Bellevue Hospital, New York.

†The terms "exploring" and "indifferent" are synonymous with "near" and "distant" as applied to the electrodes in those leads from two points on the body one of which is close to, and the other removed from, the heart

same as the algebraic sum of the differences in potential between each of these points and a third one. Clearly, the law holds regardless of the shape of the triangle formed by connecting the three points. However, with the new leads the size and the direction of the electrical axis in the sagittal plane cannot be calculated as in the frontal plane with Einthoven's triangle, for at least two reasons: first, because the source of potential is eccentrically placed in the sagittal triangle so that the precordial electrode is much closer to this source than either of the other two electrodes. In the case of Einthoven's triangle the geometric and trigonometric formulas used in the determination of the size and the direction of the electrical axis are based upon the fundamental assumption that the electrical forces generated by the heart are located at the center of the triangle. This is the same as saying that these formulas can be used only when the three points of leading in any plane are equidistant, or distant* from the heart. Second, the precordial electrode will be influenced most by those muscle elements of the heart closest to it. This is easily deduced from the change in the contour of the ventricular complex as the exploring electrode is placed on various parts of the exposed animal[3, 10, 11, 13] or human[12] heart, or on various parts of the intact animal[10, 13] or human[2, 5, 10] precordium. Because of the nature of the laws governing currents in volume conductors, those muscle elements close to the exploring electrode will cause large variations in its potential, compared with the effects of the entire heart on the distant electrode placed either on the dorsum or the left leg. The electrical variations of the first, therefore, will largely determine the form of the curve obtained.

This second point brings out a serious disadvantage of any system of leading from two points on the body, one of which is near to, and the other distant from, the heart. It is impossible to say, from an inspection of the curves obtained, which deflections arise from the potential variations of the exploring electrode, and which from the potential variations of the indifferent one. However, the former may be freed of the effects of the latter, as demonstrated by Wilson and his associates, either indirectly by calculation, or directly by making use of an indifferent electrode known to be at zero potential.

Wilson[9] showed that the potential V of any apex of Einthoven's triangle is proportional to the cosine of the angle θ made by the electrical axis with the line drawn from the center of the triangle to the

*Distant as well as equidistant, because the potential of a point in an infinite, homogeneous conducting medium varies inversely as the square of the distance between this point and the source of the potential. As this distance is increased, the corresponding fall in potential of the point in question becomes negligible. For practical purposes the human body may be regarded as a large, homogeneous, conducting medium (see Wilson, Einthoven).

apex in question. By converting θ into terms of α (the angle made by the electrical axis with the horizontal) Wilson, Macleod, and Barker[14] obtained an expression for the potential of the left leg, namely,

$$V_F = \frac{e_2 + e_3}{3},$$

where e_2 and e_3 represent simultaneous deflections in standard Leads II and III. With the aid of this expression it is easy to see how similar ones for the potential of the precordium and of the back, in terms of both the standard and the special leads, may be obtained.

If e_4, e_5, and e_6 represent the deflections in Leads IV, V, and VI, respectively, and V_P, V_B, and V_F, the potentials of the precordium, the back, and the left leg (apices of the sagittal triangle), then

$$^{*}e_4 = V_B - V_P \quad (1)$$
$$e_5 = V_F - V_P \quad (2)$$
$$e_6 = V_F - V_B \quad (3)$$

Since, as was shown, and will be further demonstrated, Lead V equals Lead IV plus Lead VI,

$$e_5 = e_4 + e_6 \quad (4)$$
$$\text{and } (V_F - V_P) = (V_B - V_P) + (V_F - V_B) \quad (5)$$

Two expressions for the precordial potential and one for the back potential are therefore:

$$-V_P = e_4 - V_B \quad (6)$$
$$-V_P = e_5 - V_F \quad (7)$$
$$-V_B = e_6 - V_F \quad (8)$$

In terms of five of the six leads, these become:

$$-V_P = e_4 + \left\{ e_6 - \frac{e_2 + e_3}{3} \right\} \quad (9)$$

$$-V_P = e_5 - \frac{e_2 + e_3}{3} \quad (10)$$

$$-V_B = e_6 - \frac{e_2 + e_3}{3} \quad (11)$$

It is entirely unnecessary to calculate potentials in this manner, however, since they may be simply and rapidly obtained by the direct method first described by Wilson, Macleod, and Barker in 1932, and further elaborated in 1934.[1] With this direct method an attempt has been made to demonstrate the quantitative and qualitative effects of the potential variations of a distant electrode on the curve obtained when this electrode is paired with one on the precordium, as is done in Leads IV or V of Wolferth and his associates.

*The minus sign is placed before V_P in Leads IV and V because the more negative (electrically speaking) the potential of the precordium compared to the back and left leg, the more positive (directionally speaking) will be the corresponding deflection in those leads. Similarly, the more negative the back with respect to the left leg, the higher will be the deflections in Lead VI.

METHOD

Nine subjects whose standard electrocardiograms showed widely varying electrical axes in the frontal plane were selected. The clinical diagnoses in these and a brief summary of each are given in Table I. The essential electrocardiographic features in the standard leads were as follows: atypical right bundle-branch block in two; left bundle-branch block in one; a deep Q in Lead I with a QRS interval of 0.114 sec. in one; a Q_1T_1 type of curve associated with infarction of the anterior wall of the heart in two, one of which also showed a QRS interval of 0.110 sec.; one each of right and of left deviation of the electrical axis with QRS intervals less than 0.1 sec.; and, finally, one electrocardiogram normal in all respects except for slight deviation of the electrical axis to the left.

On each subject a series of nine electrocardiograms were taken simultaneously with standard Lead I in the following order: three standard leads with the galvanometer string at normal sensitivity (1 cm. equals 1 mv.); Leads IV, V, and VI of Wood and Wolferth; and finally the potentials of the precordium (V_P), the back (V_B), and of the left leg (V_F). In order to have comparable curves, the last six, with one exception, were taken with the galvanometer string at half-normal sensitivity (1 cm. equals 2 mv.). All curves were taken with the patients in the sitting position. Leads IV, V, and VI were taken in the usual way. The right arm electrode was placed in the fifth intercostal space in the left midclavicular line, the left arm electrode just medial to, and below, the inferior angle of the left scapula with the patient's arm at his side, and the left leg electrode on the left lower leg. The potentials of these three points were then obtained by pairing each in succession with an indifferent electrode, connected through separate, fixed, noninductive resistances of 5,000 ohms to the right arm, the left arm, and the left leg, respectively. The potential of such an electrode has been proved by Wilson, Johnston, Macleod, and Barker[1] to be practically at zero potential throughout the cardiac cycle. The mechanics in taking the potentials were such that in the finished record positivity of the exploring electrode was represented by a downward deflection. Early in the experiments it was learned that the precordial electrode had to be held at precisely the same point while recording Lead IV, Lead V, and the potential of the precordium (V_P), for otherwise the relationships discussed above did not hold. This fact emphasizes the marked effects on the precordial electrocardiogram of even the slightest movement of the exploring electrode.

The electrodes used on the extremities were of German silver wrapped in flannel wet with saturated saline. On the precordium and back the electrodes consisted of a piece of sponge soaked in

TABLE I

SUMMARY OF CASES STUDIED

CASE NUMBER AND INITIALS	AGE	SEX	COLOR	RECEIVING DIGITALIS	ESSENTIAL FEATURES OF STANDARD ELECTROCARDIOGRAMS	CARDIAC DIAGNOSIS*
1 J. R.	59	M	W	No	Q_1T_1 type	(a) Arteriosclerosis and unknown (b) Enlarged heart, coronary sclerosis, thrombosis of left coronary artery, recent infarction of myocardium (c) Regular sinus rhythm (d) IIa
2 M. F.	55	M	W	Yes	Atypical right bundle-branch block with tall R and deep, broad S in Lead I. QRS interval of 0.160 second	(a) Hypertension and arteriosclerosis (b) Enlarged heart, arteriosclerosis with dilatation of aorta (c) Regular sinus rhythm, atypical right bundle-branch block (d) IIb
3 O. P.	37	M	B	Yes	Left deviation of electrical axis T-waves inverted in Leads I and II	(a) Hypertension and syphilis (b) Enlarged heart, aortitis with aneurysm of aortic arch (c) Regular sinus rhythm, pulsus alternans (d) IIb
4 S. S.	52	M	W	Yes	Left bundle-branch block. Low, vibratory, ventricular complexes in all three leads. QRS interval of 0.174 second	(a) Arteriosclerosis and hypertension (b) Enlarged heart, coronary sclerosis, arteriosclerosis with dilatation of aorta (c) Regular sinus rhythm, left bundle-branch block, ventricular premature contractions (d) III

TABLE I—CONT'D

CASE NUMBER AND INITIALS	AGE	SEX	COLOR	RECEIVING DIGITALIS	ESSENTIAL FEATURES OF STANDARD ELECTROCARDIOGRAMS	CARDIAC DIAGNOSIS*
5 J. O'D.	49	M	W	No	Q_1T_1 type. QRS interval of 0.110 second	(a) Arteriosclerosis (b) Coronary sclerosis, myocardial fibrosis, thrombosis of left coronary artery, recent infarction of myocardium (c) Regular sinus rhythm, incomplete left bundle-branch block, paroxysmal supraventricular tachycardia with ventricular aberration (d) IIa
6 F. O'C.	18	M	W	No	Right deviation of electrical axis	(a) Congenital maldevelopment (b) Pulmonary stenosis (c) Sinus arrhythmia (d) I
7 E. C.	52	M	W	No	Atypical right bundle-branch block. Prominent R, shallow, broad S in Lead I. QRS interval of 0.122 sec.	(a) Arteriosclerosis, previous hypertension, emphysema (b) Enlarged heart, arteriosclerosis with dilatation of aorta (c) Sinus tachycardia, atypical right bundle-branch block (d) IIa
8 F. F.	70	F	W	No	Deep Q in Lead I. Left deviation of electrical axis. QRS interval of 0.114 second	(a) Arteriosclerosis and hypertension (b) Coronary sclerosis, myocardial fibrosis (c) Regular sinus rhythm, incomplete left bundle-branch block (d) IIa
9 D. P.	41	M	W	No	Slight deviation of electrical axis to left	No heart disease

*Cardiac Diagnoses made in accordance with "The Criteria for the Classification and Diagnosis of Heart Disease" of the New York Heart Association.

saturated saline placed in the end of a small test tube where it made contact with a German silver plate. These electrodes had to be held in place by an assistant. Their area of contact with the chest or back was roughly circular, about 1 cm. in diameter.

Two galvanometers were used. One (upper string in illustrations) was a Hindle No. 2 (Cambridge Instrument Co., Inc.) with a string resistance of 4,000 ohms. In circuit with it was a single stage, vacuum tube amplifier,* which made it possible to take all special leads without changing the tension of the galvanometer string. The other machine was a Hindle No. 3 (Cambridge Instrument Co., Inc.), also with a string resistance of 4,000 ohms. It was placed perpendicular to the first machine and its string shadow was deflected by means of a plane mirror into the camera slit. In only one instance was parallax present with this arrangement. The second instrument was used in the ordinary way to record standard Lead I at either one-half, three-fifths, or full sensitivity of the string, depending upon the size of the

TABLE II

Values in tenths of a millivolt of deflections in special leads occurring simultaneously with various points in standard Lead I, indicated in the second column. Lead IV, Lead V, and Lead VI are those described by Wood, Bellet, McMillan, and Wolferth. V_P and V_B are the potentials of the same points on the precordium and on the back respectively, used in taking Lead IV. V_F is the potential of the left leg.

CASE NO.	STANDARD LEAD I	LEAD IV (V_B-V_P)	LEAD V (V_F-V_P)	LEAD VI (V_F-V_B)	V_P	V_B	V_F
1	0.035 sec. after peak of Q	17.2	8.2	-10.2	-12.0	5.8	-5.1
	Peak of T	4.2	5.6	1.8	- 4.4	0	0.8
2	Peak of R	-9.6	-9.8	0	12.2	0.8	1.5
	Peak of S	3.2	5.2	1.8	-6.6	-2.4	-0.8
	Peak of T	0.5	0	-0.6	-0.2	0.8	0.4
3	Peak of R	-43.6	-45.4	0	46.0	1.6	0.4
	Peak of T	6.0	7.4	0.6	-6.0	0	0.4
4	Peak of R	34.6	23.8	-9.4	-27.4	8.0	-1.8
	End of T	-15.4	-12.0	4.0	12.0	-4.0	0
5	Peak of Q	2.4	3.2	1.4	-2.6	0	0.4
	Peak of R	13.0	0.8	-12.0	-7.2	7.0	-6.8
	Peak of T	-1.4	1.4	3.4	-0.1	-0.5	1.1
6	0.015 sec. after peak of S	22.0	27.2	5.2	-24.8	-1.0	4.2
	Peak of T	-14.6	-13.8	1.8	14.8	0.4	2.8
7	Peak of R	-6.0	-6.0	0	5.2	0	-0.4
	Peak of T	-1.6	-1.6	0	2.0	0.4	0.4
8	Peak of Q	2.2	4.2	2.4	-3.2	-0.6	1.6
	Peak of S	6.4	7.2	0.8	-6.4	-0.4	0
	Peak of T	-6.0	-6.0	0	6.0	0	0
9	Peak of R	-16.8	-16.0	0.4	18.8	1.4	1.6
	Peak of T	- 8.0	- 6.2	1.0	7.2	-0.2	0.8

*The authors are indebted to Dr. Franklin D. Johnston, of the University of Michigan Medical School, for designing and constructing this amplifier.

deflections (lower curve in all illustrations). Simultaneous points in various leads were determined with the aid of a comparator designed by Capt. Elliott and manufactured by the Cambridge Instrument Co., Inc. The points selected were those that seemed most likely to show a very high deflection in all special leads, and they varied in each subject (Table II).

Where it was possible to identify the "intrinsic deflection," the time of this with respect to the beginning of the ventricular complex in standard Lead I was measured with the comparator. Used by the same operator, the error with this instrument was not greater than ± .003 sec.

RESULTS

Table II shows the values obtained for simultaneous deflections in Leads IV, V, and VI, and for the corresponding potentials of the precordium (V_P), the back (V_B), and the left leg (V_F). In measuring these, it was necessary to select the proper sign before the figures. In the leads taken according to the method of Wood and Wolferth, an upright deflection was positive, and a downward deflection, negative. The reverse, however, was true for the point potentials, because the hook-up to the galvanometer was such that a positive variation in potential was represented in the finished record by a downward movement (see footnote p. 700).

If the columns in Table II headed "Lead IV," "Lead V," and "V_P" are compared, the quantitative effects of the potential variations of the back and of the left leg upon those of the precordium can be seen at a glance. The greatest difference between simultaneous potentials in Lead IV and in V_P was 0.72 mv. (Case 4). The greatest difference between simultaneous potentials in Lead V and V_P was 0.64 mv. (Case 5). The mean difference, without regard to sign, in the nine cases between twelve simultaneous, initial ventricular deflections in Lead IV and in V_P was 0.28 mv. The mean difference between these same deflections in Lead V and V_P was 0.23 mv. Clearly, the average effect of the indifferent electrode, whether it be on the left leg or on the back, is small; the important point to be emphasized is that this effect is extremely variable.

The qualitative effects of the indifferent electrode are apparent in Figs. 1 to 6. It is very easy to see that in every instance the potential of the precordium (V_P) dominated the curve obtained when this point was paired either with the back or the left leg (Lead IV or Lead V). This may not be true, however, if the precordial potential is small (see *discussion*).

The figures in Table II bear out the truth of the law Lead V = Lead IV + Lead VI, although in one instance there is a discrepancy

as large as 0.18 mv. (Case 3). Two reasons were most important in determining small differences: first, a point occasionally selected in standard Lead I for measurement was found to be simultaneous with a rapidly changing deflection, almost vertical in extent, in one or several of the special leads. The difficulties in measuring the exact

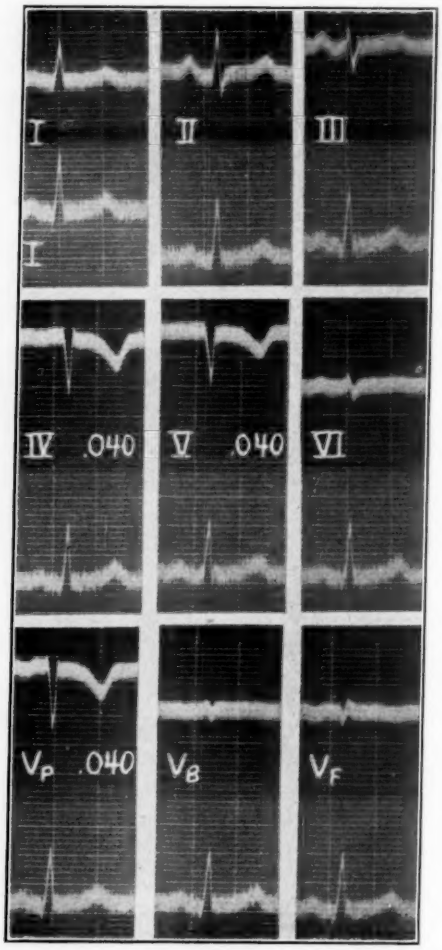

Fig. 1.—Case 9. No heart disease, slight left deviation of the electrical axis. The lower curve in each record is standard Lead I taken with the galvanometer string at normal sensitivity (1 cm. equals 1 mv.). The upper curves in the first three records are, *I*, standard Lead I; *II*, standard Lead II; *III*, standard Lead III. These also were taken with the string at normal sensitivity. The upper curves in the last six records were taken with the string at half-normal sensitivity (1 cm. equals 2 mv.), and are as follows: *IV*, *V*, and *VI* are Leads IV, V, and VI of Wolferth and his associates. V_P, V_B, and V_F are the potential variations, determined by the method of Wilson, of the following points; V_P, the fifth intercostal space in the left midclavicular line; V_B, the back just medial to, and above, the inferior angle of the left scapula; V_F, the left leg. Precisely the same points were used in taking Lead IV as in taking the potentials of the precordium (V_P) and of the back (V_B).

The figures written on the curves give the interval between the first QRS deflection in Lead I, and the beginning of the chief upstroke (intrinsic deflection) in the upper curve.

In all subsequent illustrations, the symbols and figures have the same significance. Unless otherwise stated, the string sensitivity is also the same. The time lines on all curves indicate one-fifth of a second.

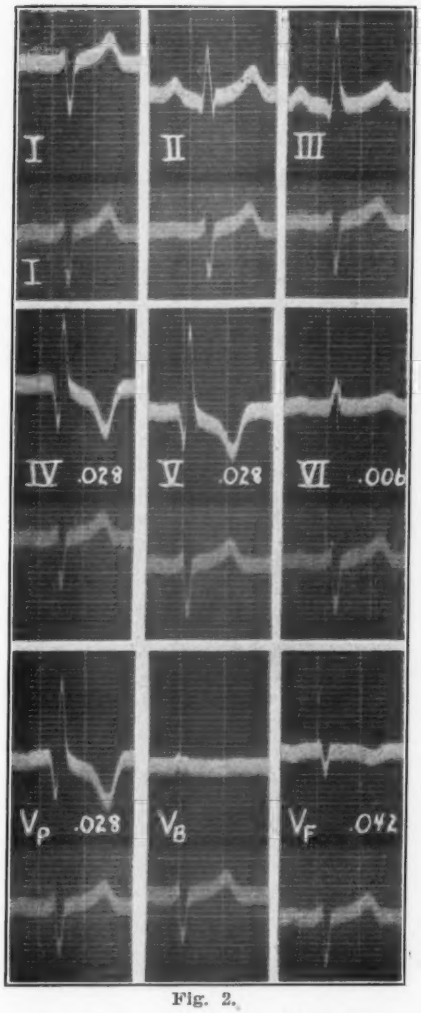

Fig. 2.

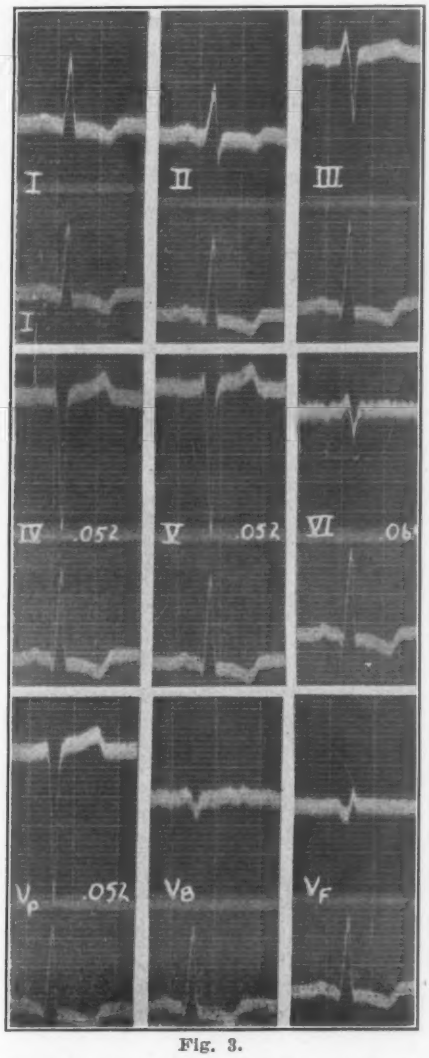

Fig. 3.

Fig. 2.*—Case 6. Congenital pulmonary stenosis, right deviation of the electrical axis. The lower curve (Standard Lead I) in the first record was taken with the galvanometer string at approximately three-fifths normal (1 cm. equals 0.6 mv.). In subsequent curves it is recorded at half its normal amplitude.

Fig. 3.*—Case 3. Hypertensive and syphilitic heart disease with aneurysm of aorta, left deviation of electrical axis. Lower curves in all records are three-fifths of normal amplitude.

*In the first record of Fig. 2, and also of Fig. 3, it will be noted that although the upper curve was taken with the string at normal sensitivity and the lower one with the string at three-fifths normal; nevertheless the curves have approximately the same amplitude. The reasons for this are twofold: first, the upper string was connected with the output terminals of a vacuum tube amplifier, as described in the text, and the lower string was used in the ordinary way. With this arrangement, when Lead I was taken simultaneously on both strings, short circuiting through the second was such that the amplitude of the deflections recorded by the first was reduced by approximately 30 per cent. Second, it was discovered after completion of these experiments that the resistance box of the lower string was inaccurate. Compared with the deflection caused by a known, standard milliampere, the deflection resulting from movement of the smaller, compensating resistance knob through one division was only nine-tenths as large. Therefore all waves recorded by this string were too large by approximately 10 per cent. When the upper curve was recorded at normal string sensitivity, and the lower at three-fifths normal, it is easy to see how these two factors caused the size of the curves to approach each other.

The amplitude of the special leads was entirely correct, since the resistance box of the galvanometer used to record them was accurate.

size of such a deflection even with the aid of a comparator are not hard to imagine. Second, precordial electrocardiograms, more especially those taken with the exploring electrode close to the apex of the heart, vary with respiration. Although simultaneous points in several ventricular complexes were measured in every case, and a mean value was determined, some error on this score was unavoidable. For similar

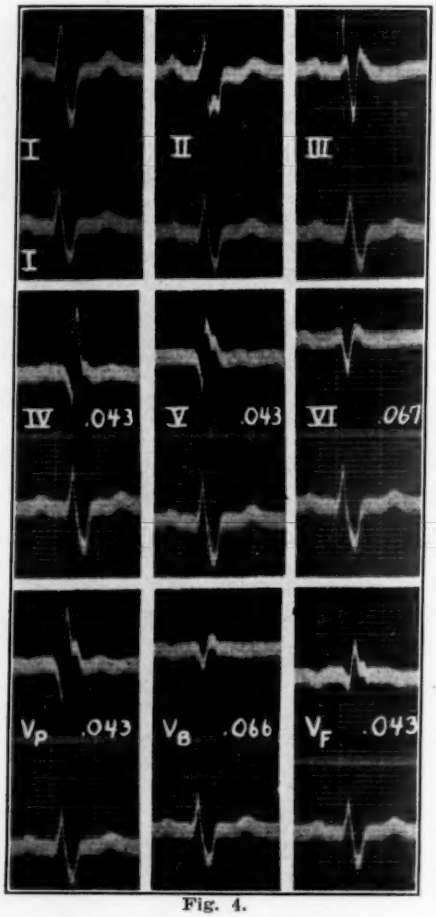

Fig. 4.

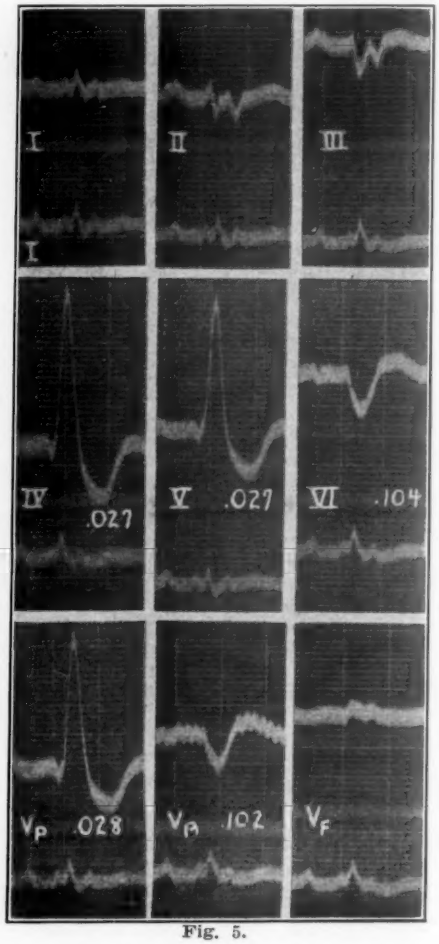

Fig. 5.

Fig. 4.—Case 2. Hypertensive and arteriosclerotic heart disease, atypical right bundle-branch block (QRS interval 0.160 sec.). The potential of the left leg, V_F, is at normal amplitude rather than at half-normal as are the special leads in the remainder of this and in all other illustrations.

Fig. 5.—Case 4. Arteriosclerotic and hypertensive heart disease, left bundle-branch block (new terminology; QRS interval 0.174 sec.).

reasons Leads IV, V, and VI were not exactly the same as $(V_B - V_P)$, $(V_F - V_P)$ and $(V_F - V_B)$, respectively. A third factor enters here, namely, slight movement of the precordial electrode, which, as has already been pointed out, may cause very marked changes in the curve obtained.

The time of the intrinsic deflection (chief upstroke) of the special leads compared with the earliest initial ventricular deflection in Lead I was measured whenever it could be identified. The results are given

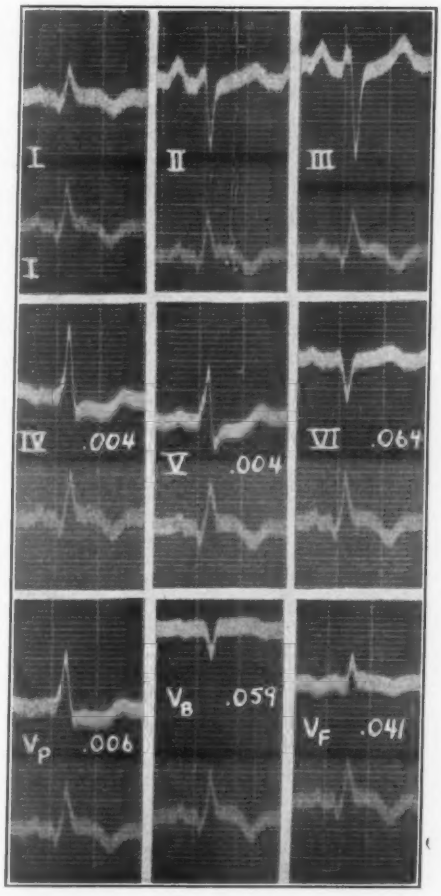

Fig. 6.—Case 5. Recent infarction of the anterior wall of the left ventricle, QRS interval 0.110 sec.

TABLE III

Intervals between the intrinsic deflection (chief upstroke) of the special leads and the earliest, initial, ventricular deflection in standard Lead I. The symbols have the same significance as in Table II.

CASE NO.	IV	V	VI	V_P	V_B	V_F
1	0.009	0.005	0.054	0.006	0.055	0.034
2	0.043	0.043	0.067	0.043	0.066	0.043
3	0.052	0.052	0.064	0.052	–	–
4	0.027	0.027	0.104	0.028	0.102	–
5	0.004	0.004	0.064	0.006	0.059	0.041
6	0.028	0.028	0.006	0.028	–	0.042
7	0.038	0.038	0.049	0.036	–	–
8	0.029	0.032	0.048	0.030	–	0.020
9	0.040	0.040	–	0.040	–	–

in Table III. In Lead IV, Lead V, and V_P, the chief upstroke began at practically the same time. Apparently the time of this deflection in the first two was not influenced by electrical variations of the distant electrode, for it will be noted that the chief upstroke was usually later in V_F and V_B than in V_P. When the intrinsic deflection could be identified in V_B, its time was approximately the same as that of the analogous deflection in Lead VI.

DISCUSSION

It is not meant to imply that the many methods of taking precordial electrocardiograms now in use are not of diagnostic value to those familiar with the normals of such methods. Few of these, however, have established a standard size for the exploring electrode, or a definite location for it on the precordium, both of which factors have a tremendous influence on the electrocardiograms obtained. Furthermore, by all of these methods, leads are taken from two points on the body, the resulting curve representing the difference in potential between them. Since one point is usually closer to the heart than the other, it is impossible to determine, by inspection of the curve, the size or direction of the potential variations of either. It would seem that if additions are to be made to our knowledge of the electrophysiology of the heart, the method of approach must be simplified so that the potential of a single point can be studied, rather than the difference in potential between two points. All this was very well known to Wilson and his associates when they designed the method used to carry out the work reported here.

It has been pointed out repeatedly by Wolferth[6, 16] and by Roth[17] that although Leads IV and V usually resemble each other, this is not always true. From what has been presented, the reason seems obvious. When discrepancies occur, they are due to considerable differences in the potential variations of the back compared with those of the left leg, provided that the precordial electrode has not been moved while taking these two leads. Theoretically, this should be most common in patients with myocardial infarction near the base of the anterior wall of the left ventricle.

Case 5,* Fig. 6, is an example. The precordial electrode, placed over infarcted muscle, was negative (V_P). The left leg (V_F) also showed a negative potential, but the peak of its curve came very much

*This patient came to necropsy three and one-half months after the curves shown in Fig. 6 were recorded. The heart weighed 700 gm. More than half of the anterior surface was made up of left ventricle. The parietal pericardium was adherent to the bulging anterolateral aspect of this chamber. There was extensive, old infarction of the entire left apex, the apical four-fifths of the anterior and lateral walls of the left ventricle, and the apical four-fifths of the anterior third of the interventricular septum. The endocardial surface of the infarcted area was covered with a thick, organizing mural thrombus.

There was marked atherostenosis of the first 2.5 cm. of the anterior descending branch of the left coronary. The remaining lumen was occluded by an old, partially canalized thrombus.

later than that of the precordial potential, indicating a different origin. This peak was simultaneous with, and therefore responsible for, the inverted deflection in the QRS complex of Lead V since there is only a suggestion of such a deflection in the precordial potential, V_P.

A striking experimental example of this can be seen in the article by Wilson and his associates[15] on myocardial infarction produced in dogs by ligation of the septal branch of the left coronary artery. In *Fig. 4*, on page 601 of that article, the potential variations of the left hind leg are very much larger than those of several precordial points. The effects of pairing each of the precordial points with the left hind leg are shown in *Fig. 5* on the next page. The curves thus obtained are decidedly dominated by the potential variations of the left hind leg, and are very different from those representing the true precordial potentials.

A clinical example of a precordial electrocardiogram dominated by potential variations of the distant electrode was not seen in this small series, and it would seem unlikely that such an extreme situation ever exists in humans. However, the many curves thus far published, showing marked differences between Leads IV and V, are evidences of the extent to which potential variations of the distant electrode may distort the precordial electrocardiogram.

In this group, Case 2, Fig. 4, is an example. Leads IV and V differ considerably from each other and from the true precordial potential, V_P. An important point is brought out by these electrocardiograms. The prominent notch on the descending limb of the QRS of V_P is almost absent in Lead IV. The reason for this is apparent if V_B is examined. The last QRS deflection in this curve is upward. With the comparator it was discovered that this was simultaneous with the notch seen in V_P. Since both are approximately the same size, and since both represent simultaneous negative variations in potential of the two points concerned, then when the difference in potential between these was taken (Lead IV), the notch practically disappeared. The reverse occurred in one instance (Case 1). Both slurring and notching in Lead V were due to potential variations of the left leg, rather than of the precordium.

SUMMARY AND CONCLUSIONS

The qualitative and quantitative effects of the potential variations of the distant electrode in Leads IV and V of Wolferth and his associates have been demonstrated with the aid of an indifferent electrode shown by Wilson and his coworkers to be at zero potential throughout the cardiac cycle. The potential variations of the left leg, or of a point on the back, medial to, and just below, the inferior angle of the left scapula, were usually small compared with the potential variations

of the precordium. In the cases studied, the latter dominated the form of the electrocardiogram obtained when the precordium was paired with either the point on the back or the left leg, as in Leads IV and V.

The time of the "intrinsic deflection," when this could be identified, was usually the same in Lead IV, Lead V, and in the curve representing the potential of the precordium. Slurring and notching in electrocardiograms obtained by leading from two points on the body may be due to potential variations of the distant electrode. If the position and size of the exploring electrode are kept constant, marked differences between Leads IV and V can be due only to considerable differences between the potential variations of the back and the potential variations of the left leg.

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HEMICONSTRICTION OF THE VASCULAR SYSTEM ASSOCIATED WITH CEREBRAL DISEASE*

WM. J. KERR, M.D., AND FRANKLIN J. UNDERWOOD, M.D.
SAN FRANCISCO, CALIF.

IT IS generally recognized that patients with hemiplegia may exhibit changes in temperature, color, and sweating of the paralyzed extremities and that edema of the involved limbs may be present. Within the past few years there has been renewed interest in these phenomena, especially in view of the work of J. F. Fulton and his associates,[1] who have observed and studied vasomotor effects of central origin, in the course of their investigation concerning the functions of the premotor area of the cortex. Following ablation of this area in monkeys, they have consistently observed vasomotor phenomena in the contralateral extremities, and they consider these autonomic effects to constitute one of the characteristics of the "syndrome of the premotor area." Both experimentally and clinically, however, it is extremely rare in hemiplegic limbs to find a marked diminution in the blood pressure and in the pulsations of the major arteries of the affected side. During the past two years we have been fortunate in being able to study a patient who has a remarkable hemiconstriction of the vascular system associated with cerebral disease of the opposite hemisphere.

CASE REPORT

H. M., a thirty-three-year-old American clerk, entered the University of California Hospital for the first time in April, 1934, with the chief complaint of convulsive seizures of nine years' duration. He had been well until the age of twenty-three, ten years before entry. At that time he developed an infected right lower molar tooth. A week prior to the extraction of the tooth he complained of a very severe frontal headache lasting for one day. Following the extraction, he partook of considerable alcohol, and two days later after drinking excessively at a party he became unconscious, but awakened the following morning feeling well and remained so until noon when he again fainted while at work. During the ensuing week he felt well, then he awakened one morning feeling confused and drowsy and was unable to speak. This motor aphasia persisted, and two days later he was transferred to the Methodist Hospital in Omaha, Neb. Two days after arriving there, he first noticed that the right side of his face, his right arm, and right leg were paralyzed. A letter from the Methodist Hospital informs us that he had a very typical motor aphasia with the usual findings of right hemiplegia. His temperature was normal, and his pulse varied between 55 and 60. His spinal fluid pressure was slightly over 200 mm. of water, and there were 25 cells per cubic millimeter, 92 per cent of which were lymphocytes. The Lange curve was 3345410000, and the blood and spinal fluid Wassermann tests were negative. It was the impression of Dr. G. Alexander Young

*From the Department of Medicine, University of California Medical School.

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that the patient's lesion was in the left lower central parietal region, and the pathological process was considered to be one of three: a focal encephalitis, a cerebral abscess or a tumor. After eight weeks in the hospital his speech and muscle power had begun to return. He noticed at this time that his right side was cooler

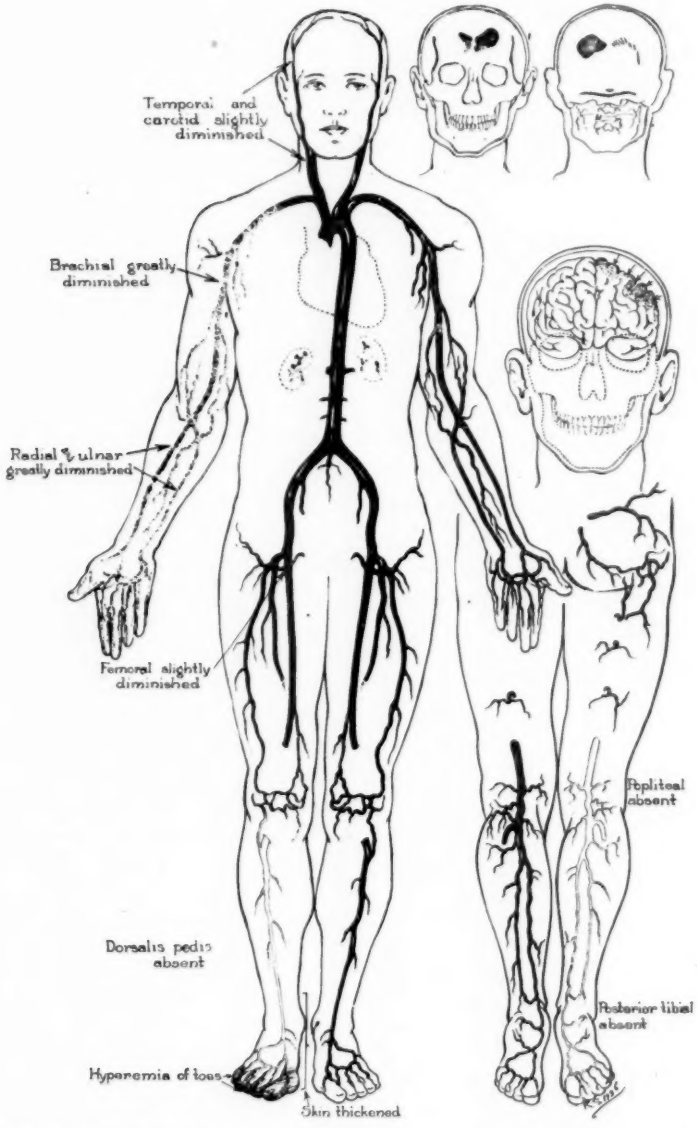

Fig. 1.—Illustrating the unilateral vasoconstriction, and the region of the brain affected.

and perspired less than his left. Also he observed that the pulse at his right wrist was weak, and at times could not be felt. One year after discharge from the hospital there was little residual paralysis, and speech had returned fairly well. At this time he had a short "fainting spell" on one occasion, and several weeks later he had his first jacksonian seizure, initiated by involuntary contraction of his right arm,

and rotation of the head to the right, followed immediately by unconsciousness and convulsions. After this time he had several seizures a year, and on one occasion in 1928 he had a series of fifteen successive convulsive attacks. Between 1928 and 1934 he had only two seizures, the last occurring two weeks before entry. All of the seizures have been similar, beginning with forcible raising of his right arm, and with sudden rotation of the head to the right, followed by unconsciousness and convulsions lasting for several minutes, and associated with the biting of his tongue

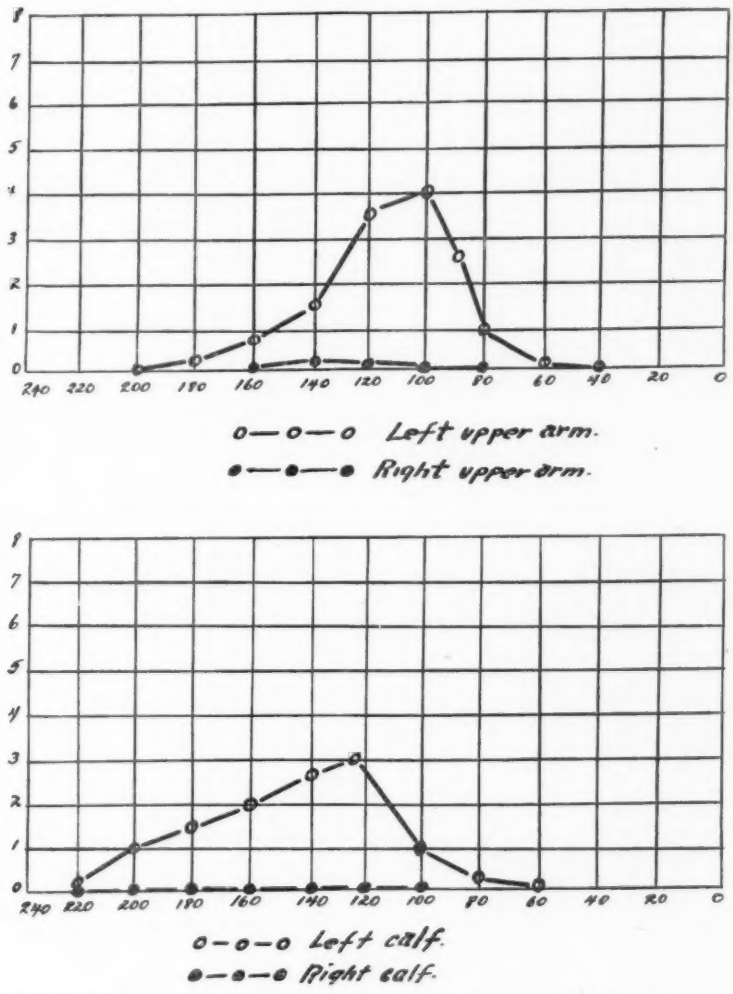

Fig. 2.—Oscillometry, showing no oscillations in the right extremities.

but without loss of sphincter control. During this entire time the patient's radial pulse on the right side has remained feeble or absent. There has been some variation in amplitude observed by him. At times the pulsation may be easily felt, but it has never been equal to the left radial pulse. He has had mild intermittent claudication in the right leg, and there has been slight edema of the ankle. He observed that his entire right side was cooler, and that it perspired less freely than the left side.

On physical examination in 1934 it was noted that he had a slight slurring and difficulty in speech, although the action of his palate and his tongue was normal.

The right facial muscles were definitely weak. The motor power of all extremities was good but was slightly less on the right than on the left, and the movements of the right arm and leg were noticeably clumsy. There was moderate atrophy and spasticity of the right limbs, and their reflexes were hyperactive. He had a sustained ankle clonus and Babinski sign on the right. The most striking finding on physical examination was that the radial and brachial pulsations were barely perceptible on the right side, and the popliteal, dorsalis pedis, and posterior tibial arteries could not be felt to pulsate on that side. The pulsations of the temporal, carotid, and femoral arteries were found to be very slightly diminished on the affected side (Fig. 1).

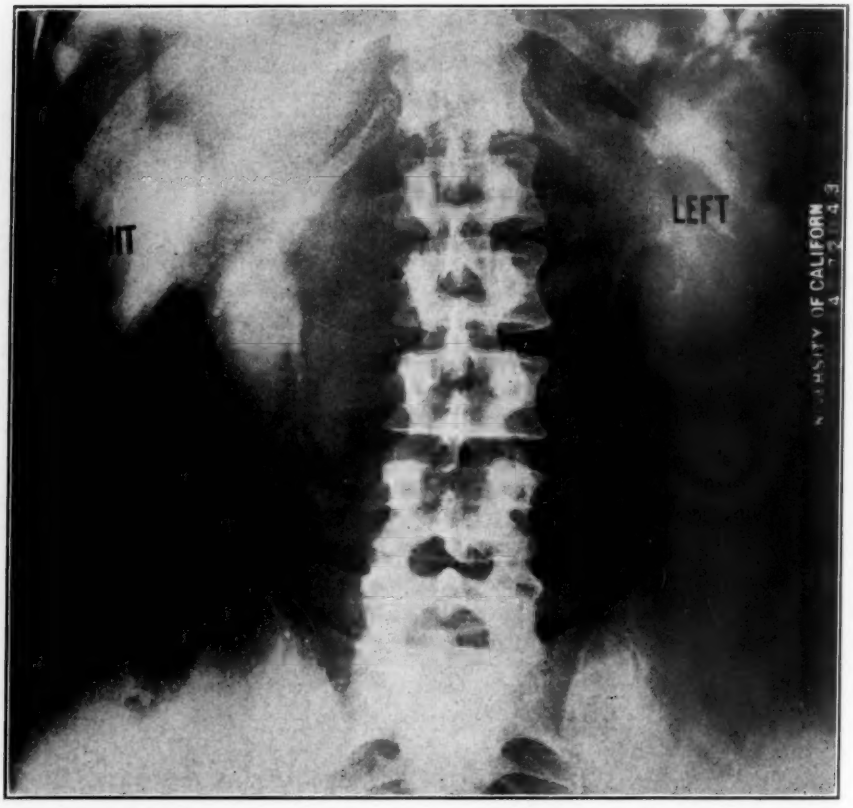

Fig. 3.—Intravenous pyelograms, showing right pelvis and calyces reduced in size as compared with those of the left kidney.

There appeared to be no difference in the retinal arterioles of the two sides. The blood pressure could not be obtained in the right arm and leg by the usual method. The skin of the extremities on the affected side was slightly cooler and drier than that of the normal side, and there was the peculiar thickening and hypertonus of the skin on the right side that one of us (Wm. J. K.) has frequently observed with lesions of the spinal cord; this effect presumably resulting from interference with the autonomic fibers supplying the skin.* There was slight edema of the right ankle, and, when the leg was held in a dependent position, there was considerable cyanosis of the toes. The pulsations of the major arteries on the left side were all of

*This will be the subject of a report by Wm. J. Kerr, M.D., and Charles A. Noble, Jr., M.D.

good amplitude; however the vessels were distinctly thickened and tortuous; and the blood pressure was elevated (180/110 left arm, and 210/120, left leg).

Course.—Since the patient's first admission in 1934 there has been essentially no change in his neurological status. He has had three jacksonian seizures, the last occurring in March of this year. It is of interest that toward the end of this last convulsion, and for at least twenty minutes thereafter, his wife observed that his pulse at the right wrist was much more easily felt than usual, although it was still not equal in amplitude to that of the left. Other than for this observation there has been no noticeable change in arterial pulsations; however, there has been considerable change in the appearance of the right foot. Whereas in 1934 the patient's chief complaint was the convulsive state, now it is related to the disability from his right lower extremity. When he hangs his foot in a dependent position there now occurs

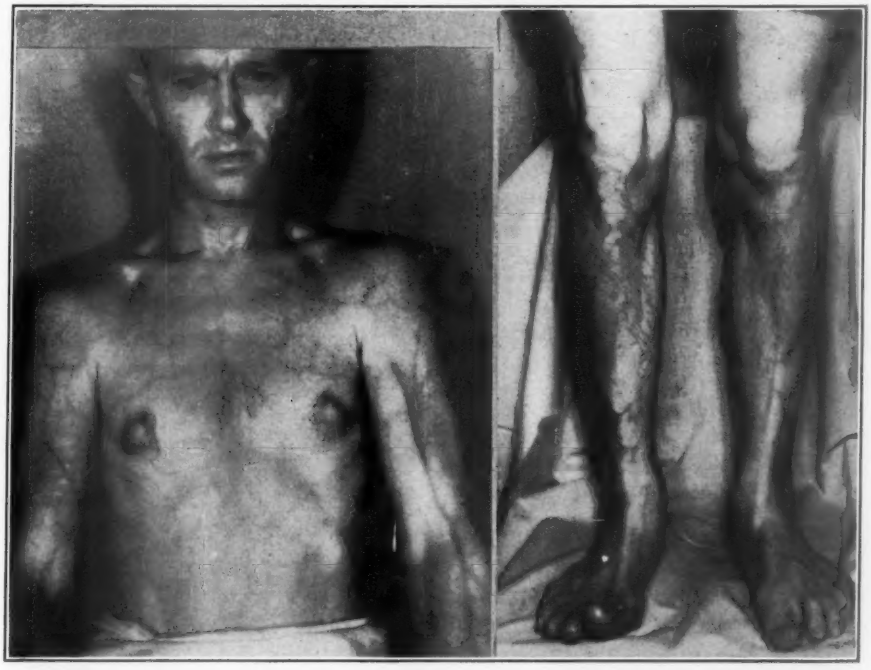

Fig. 4.—Infra-red photographs, showing the increased venous markings on the right side, as compared with those on the left. The hyperemia of the toes and glossy appearance of the skin are also illustrated.

a remarkable reddish blue hyperemia of the toes, similar to that seen in thromboangiitis obliterans. The toenails of the right foot have become thickened and brittle. The skin of the foot is thickened and glossy, and on one occasion he developed small patches of scleroderma on the ankle and calf. On numerous occasions he has had thrombophlebitis of some of the smaller veins in the right lower leg. Eight months ago he first noticed a callus on the ball of his right foot. This became infected and was drained, but it failed to heal properly and still caused him considerable discomfort. As before, we are unable to obtain his blood pressure by the usual method; however, by the "two cuff" method it has been determined to be 118 mm. systolic in the right arm as compared to 160 in the left arm, and only 90 in the right leg as compared to 196 in the left leg. By oscillometry there were found to be no oscillations in the right extremities, whereas in the left extremities the curve was essentially normal (Fig. 2).

Laboratory Data and Special Procedures (Table I).—The fact that nearly all of the major vessels of the right side are affected to some degree is, in itself, good evidence against there being any extrinsic peripheral mechanism responsible for the vascular changes; however, by means of x-ray films of the cervical spine we excluded cervical rib. A film of the chest showed normal heart and lungs, and no evidence of anomalous vessels. Films of both arms showed no evidence of calcification in the arteries, and the bones appeared normal. It is of interest that intravenous pyelograms showed a small right kidney with pelvis and calyces reduced in size as compared with the left kidney (Fig. 3).

Our second group of studies was concerned with vasomotor phenomena. Skin temperatures were slightly lower on the right than on the left side, and the rise with spinal anesthesia was not quite as great in the right leg as in the left. The pulsations of the vessels still could not be felt after spinal anesthesia. There was, likewise, no increase of pulsations on the right side during deep anesthesia with ether. Exercise, immersion of the extremities in warm water, and inhalation of amyl nitrite made no appreciable difference in arterial pulsations. Assuming that the increased pulsations noted during his last convulsion might be due to increased blood pressure, we attempted to reproduce this condition by giving the patient 1 c.c. of 1:1,000 adrenalin (intramuscularly), and somewhat to our surprise we found that, although there was the usual marked rise in the left extremities, there was no appreciable change in the blood pressure of the right arm and leg. Pilocarpine (10 mg.) seemed to increase slightly the pulsations in the right radial artery. The sweating induced by this drug was approximately equal on the two sides. The histamine flare test was equal and normal on the two sides. Infra-red photographs of the trunk and extremities showed an increased venous circulatory bed on the right side as compared with the left (Fig. 4). Arteriograms were attempted but were

TABLE I

SUMMARY OF DATA COMPARING LEFT AND RIGHT EXTREMITIES

RIGHT	DIAGNOSTIC PROCEDURES	LEFT
Arm ----------118 mm. Leg ---------- 90 mm.	Blood pressure (two-cuff method).	Arm ----------158 mm. Leg ----------196 mm.
No oscillations.	Oscillometry.	Normal.
Pelvis and calyces reduced in size.	Renal function as suggested by intravenous pyelograms.	Pelvis and calyces approximately normal.
Slightly cooler than left (av. 1-2°).	Skin temperature.	Normal.
Slightly less of a rise than on left. No change in arterial pulsations.	Skin temperature after spinal anesthesia.	Normal rise.
No change in arterial pulsations.	Exercise. Inhalation of amyl nitrite. Immersion of extremity in warm water.	Normal response.
Marked sweating. Slight increase in amplitude of radial pulse.	Pilocarpine, 10 mg. (s.c.).	Marked sweating.
No rise in blood pressure.	Adrenalin, 1:1,000, 1 c.c. (s.c).	Marked rise in blood pressure.
Normal response.	Histamine flare.	Normal response.
Thickening of dermis. Thrombophlebitis of several small veins.	Biopsy of skin (lower legs).	Normal.
Normal arterioles.	Biopsy of pectoral muscles.	Normal arterioles.

unsuccessful because of the difficulty in introducing a needle in the right femoral artery. Biopsy of the skin from the right ankle showed moderate thickening of the skin, and a small thrombosed vein with the lumen full of leucocytes, red blood cells, and fibrin. Biopsy of the pectoral muscles on both sides showed normal appearing arterioles.

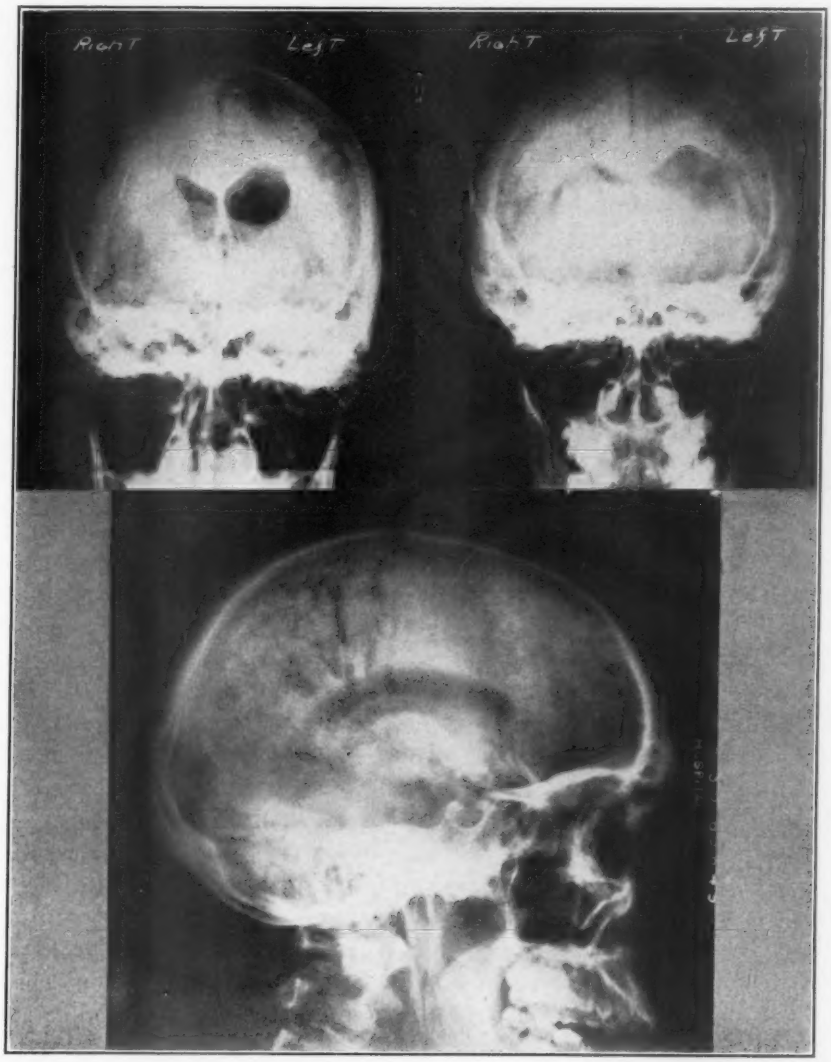

Fig. 5.—Encephalograms showing the dilated left ventricle (anterior and posterior horns), and the displacement of the third ventricle to the left. The films also show air distributed over the left cortex in dilated sulci, indicating cortical atrophy.

A third group of studies has been made to determine if possible the nature of the central lesion. X-ray films of the skull, visual fields, and spinal fluid were all normal. Encephalograms show "a unilateral dilatation of the left ventricle involving all portions of the ventricles, and the third ventricle is displaced about 4 mm. to the left of the midline. In addition, there is a large amount of air which has reached the subarachnoid space over the cerebral cortex on the left side and is distributed in

dilated sulci, which is evidence of a high degree of cortical atrophy. This is most marked in the posterior portion of the frontal lobe, and in the temporal and parietal lobes. The outlines of the right ventricle appear normal'' (Fig. 5).

DISCUSSION AND CONCLUSIONS

The etiology of this patient's cerebral lesion is not entirely clear. Cerebral thrombosis would seem to be the most plausible diagnosis. However, we assume that he has a high degree of atrophy and scarring of the left cortex. There is evidence of only minimal impairment of motor power in the right extremities, whereas the vascular changes are remarkable. In view of the work of Fulton and his coworkers, who have shown that in hemiplegia the spasticity, impairment of coordinated movements, and vasomotor phenomena are characteristic of lesions involving the premotor area, one may perhaps attribute some of the findings in our patient to involvement of the left premotor area. In this regard it is of some interest that his Jacksonian seizures begin with complex involuntary movements of the arm and head, and that, according to Fulton and Viets, this type of reaction is more typical of premotor seizures than of those arising in the motor area, in which case the seizures are more likely to begin in one muscle group and to progress in characteristic manner to other larger muscle groups.

In considering the vascular changes which this patient shows in his right extremities, we find that they are out of proportion to the muscular spasticity and weakness, and therefore cannot be attributed to atrophy and disuse of the extremities. The history suggests that there may be some degree of spasm of the arteries on the right side, inasmuch as the patient has noticed some variation in the amplitude of pulsations of his right radial artery. Also in favor of this view is the fact that pulsations were noticeably greater following an epileptic seizure; however our vascular studies indicate no evidence of spasm. In the right leg, especially, the patient now demonstrates nearly all of the findings associated with occlusive disease affecting the larger vessels, and the listing of these findings would read almost like a textbook description of thromboangiitis obliterans; namely, absent pulsations, intermittent claudication, hyperemia in dependent position, delayed reactive hyperemia, trophic changes in the skin and nails, and recurrent phlebitis. Inasmuch as the change in the arterial pulsations was observed so soon after the patient's hemiplegia, it seems quite possible that vasospasm may have been predominant for a time following the hemiplegia or may possibly have preceded it, but now there is evidence of organic occlusive arterial disease which has progressed considerably during the two years while we have observed him. He undoubtedly has developed a fairly extensive collateral circulation, and we see evidence of this in the infrared photographs.

In the literature there are many observations concerning the blood pressure in hemiplegic patients. These have been ably reviewed in a

recent article by P. C. Bucy,[2] who found that there was a great discrepancy in the findings of various observers. The blood pressure on the paralyzed side has been reported to be higher than on the normal side in some patients, and lower in others. He states that the reported findings are hard to evaluate because of the fact that normally there may be considerable difference in the blood pressures on the two sides. More consistent observations have been made concerning temperature changes, and it is fairly well established that early in the course of a hemiplegia the affected side is likely to be warmer, and later to become colder than the normal side. Bucy has reported a patient who developed a sudden right hemiplegia eight days following an automobile accident. The right arm was cold and cyanotic, and the pulse and blood pressure could not be obtained. However, over a period of days the pulse and blood pressure gradually returned to normal. In reviewing the literature he was able to find a report of only one patient with an old hemiplegia, in whom the blood pressure could not be obtained on the paralyzed side.[3]

Penfield[4] in 1933 reported thirty patients with epilepsy in whom he induced attacks by stimulating the cortex directly. Accompanying these seizures, there were interesting vasomotor phenomena occurring in the vessels of the brain, namely, arrest of visible pulsations in the arteries and engorgement of veins. Usually this vasoconstriction was quite widespread, although occasionally the arterial pulsations disappeared in a localized area, and immediately after the convulsion transient focal areas of cortical anemia could be seen. Following the seizures, the arteries pulsated violently and became bright red. Penfield observed on several occasions that with the central arterial spasm the radial pulse also disappeared completely for a short period.

Zenner and Kramer[5] have reported a patient in whom the right radial pulse could not be felt during the removal of a dural endothelioma from the left side. Osler,[6] in an article published in 1896 entitled "The Cerebral Complications of Raynaud's Disease," described a patient with aphasia and a right hemiplegia who had local asphyxia of the right hand and finally gangrene of the fingers. These and other reports suggest that a high degree of peripheral vasoconstriction may be associated with cerebral disease.

In a study of vasomotor disturbances resulting from cortical lesions, Kennard[7] has shown that after ablation of the premotor area in monkeys and chimpanzees, the skin temperature of the contralateral foot was considerably lower than that of the normal side. She made the interesting observation that if the environmental temperature was low this difference was marked, but if it was relatively high there was very little, if any, difference in skin temperatures of the two sides. She found that the vasoconstriction was prompt and equal in both feet when an operated animal was placed in a cold environment, but when it was then rapidly transferred to a warm environment there was a distinct lag in vasodilata-

tion on the affected side, thus indicating an impairment of the vasodilator mechanism resulting from ablation of the premotor cortex. Other autonomic effects observed were transient edema, changes in the color of the skin, and diminished perspiration on the affected side. No change in blood pressure was observed.

The corticospinal pathways from the premotor area have not yet been completely traced; however, the course of these fibers has been clarified considerably by the recent investigations of Hoff[8] and of Kennard.[9] Very little is known about the corresponding corticospinal autonomic pathways. They probably traverse the capsule in company with the pyramidal fibers. Hunsicker and Spiegel[10] have produced changes in skin temperature of the contralateral extremities by cortical stimulation in cats, and this effect persists after section of either the pyramidal or the extrapyramidal projection systems but disappears when both tracts are cut, indicating probably more than one pathway for vasomotor fibers. It is known, of course, that there are vasomotor centers in the hypothalamus, and it has been suggested that these are under the inhibitory control of the cortex. With destruction of the cortex, according to this hypothesis, these lower centers are "released" to increased activity, thus giving rise to vasomotor effects. As Kennard points out, it is impossible to say whether some of the effects are due to cutting off of an active vasodilator mechanism, or to the removal of an inhibitory effect on the mechanism of vasoconstriction.

Summarizing the sequence of vascular changes in our patient, we presumed that vasoconstriction of the larger vessels of his right extremity occurred following the cerebral accident. At least we can say that there was probably interference with the autonomic nerve supply to the skin and blood vessels, and that this presumably resulted from involvement of the premotor area of the left cortex.* Structural changes have now occurred in the larger arteries of the right side. Possibly the profound vasomotor imbalance incident to his hemiplegia hastened the evolution of an occlusive arterial disease. We know that even the vessels of his left side are abnormally thickened and tortuous and that he has hypertension on that side. Considering the frequency of hemiplegia and the rarity of such marked and persistent changes in pulse and blood pressure, one must probably assume some such unknown factor. Whatever the mechanism, there is evidence that the patient now has unilateral obliterative arterial disease, which simulates thromboangiitis obliterans in many respects.†

*Fulton and Kennard have reviewed the data presented and suggest that one cannot exclude other cortical areas or the subcortical nuclei from consideration in this case. Likewise, we have no proof that hemivascular constriction preceded the attack of hemiplegia. Under the circumstances the unilateral changes cannot be attributed to a premotor lesion alone.

†During the past week we have observed four patients with premotor lesions on the neurosurgical service of Dr. H. C. Naffziger. Each of these patients had been operated upon recently; two with tumors in the right hemisphere and two with traumatic lesions in the left hemisphere. In only one were there any significant peripheral changes; in this case, a young man who had suffered from a hemorrhage in the left premotor area, after being struck by a baseball and the clot evacuated, showed two weeks later greater pulsations in the vessels and some relaxation of the skin on the right (opposite) side.

SUMMARY

The case report is presented of a male, aged thirty-four years, who was found to have marked vasoconstriction of the major arteries of his right extremities, following a right hemiplegia in 1924. Jacksonian epileptic seizures beginning in the right arm likewise ensued following the cerebral accident.

Prominent findings at present are: (1) the absence of pulsations in the larger arteries of the right side, with other evidence of vascular insufficiency; (2) the finding of hypertension on the opposite (left) side; (3) encephalographic evidence of marked atrophy of the left cerebral cortex. Vascular studies indicate that vasospasm is minimal or absent, and there is evidence of unilateral obliterative arterial disease. In view of the recent observations of J. F. Fulton and his associates, it is suggested that vasomotor effects of central origin may have preceded and precipitated these changes.

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THE ELECTROCARDIOGRAPHIC CHANGES FOLLOWING CORONARY ARTERY LIGATION IN DOGS*†

BENEDICT R. HARRIS, M.D., AND RAYMOND HUSSEY, M.D.
NEW HAVEN, CONN.

THIS report concerns itself with the results of serial studies of the electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery in dogs. The series of experiments was designed primarily to correlate the various changes incident to coronary closure, viz., electrocardiographic, chemical, histologic, and surface thermometric changes. An opportunity was thus afforded of interpreting the electrocardiographic findings in the light of these other changes, as well as to study more specifically the disturbances of rhythm and the deviations of the various components of the electrocardiogram. In other articles,[1, 2, 3, 4] the chemical, histological, and surface thermometric changes are commented upon at length.

METHODS

The method of exposure and of ligation of the coronary artery is outlined in detail in a previous paper.[1] The hearts were exposed by an incision through the left fourth interspace and the anterior descending branch of the left coronary artery with its accompanying veins ligated within 2 cm. of its origin, after which the pericardium and chest wall were tightly closed. Anesthesia was obtained by the intraperitoneal injection of a 10 per cent solution of amytal in dosage varying from 0.3 to 0.5 c.c. per kilogram of body weight. The dogs employed weighed from 15 to 20 kilograms. Electrocardiograms were taken before operation, at hourly intervals for the first twelve hours after ligation, again at twenty-four hours, at daily intervals for the next week, and at weekly intervals thereafter, until the dogs succumbed or were killed. Conventional limb leads were used in all instances. Immediately after the termination of the experiments, necropsies were performed. The hearts were examined grossly for changes in consistency and appearance of the myocardium, and the coronary arteries were injected with bismuth (method of Gross) as well as carefully explored to determine whether the vessels had been completely occluded by the ligatures. Blocks of tissue were taken from the normal and infarcted zones for histologic study. Satisfactory electrocardiograms were obtained in fifty dogs and serve as the basis for the results reported.

HISTORICAL

Negativity of the T-wave in the electrocardiogram in association with experimental ligation of the coronary arteries in dogs was first described by Kahn[5] (1911). This was confirmed by Smith[6, 7, 8] (1918, 1920, 1923) in a careful serial electrocardiographic study of dogs following ligation of the coronary artery, and as another result of this

*From the Department of Pathology, Yale University School of Medicine.
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investigation he described changes in the initial deflection and the S-T segment. From clinical studies Pardee[9] (1920) stressed the S-T segment changes and described the high or low take-off of the S-T segment as particularly significant in recognizing myocardial infarction. Later, the "cove-plane" type of T-wave so frequently observed in acute and recent myocardial infarction was described by Oppenheimer and Rothschild[10] (1924). Parkinson and Bedford[11] (1928) expressed the opinion that daily variations in the characteristics of the S-T segment and T-wave deflections are of greater significance than changes in these components at any isolated interval; thus emphasizing, as Smith did, the importance of serial electrocardiographic studies in order to observe successive changes that may occur.

With these facts established, the electrocardiographic evidence of myocardial infarction became generally accepted, and attention was directed to the possibility of localizing the site of the infarction by the electrocardiogram. Parkinson and Bedford,[11] Barnes and Whitten,[12] Barnes and Mann,[13] and Crawford and his associates[14] have concluded that lesions in similar sites produce essentially the same type of curve, lesions in the left apical region anteriorly giving rise to a T_1 type of curve, whereas lesions at the posterior and basal parts of the heart give rise to a T_3 type of curve. Some doubt has been entertained regarding the specificity of these curves in localizing lesions, particularly in passing from experimental results to clinical analogy. This discussion has to do with the controversy regarding which artery may be involved, a question which seems to have been settled satisfactorily by the work of Wolferth and his associates[15, 16, 17, 18] with the use of direct chest leads. Barnes and Whitten[12] suggest that the apparently contradictory results may be due to a difference between the coronary circulation of the dog and man. Further consideration must also be given to the variations in the distribution of the coronary arteries and their branches.

Electrocardiographic studies in conditions not associated with coronary artery occlusion, such as rheumatic fever, pneumonia, pericarditis with effusion,[19-28] clearly indicate that the T and R-T changes are not specific for coronary closure and may be encountered occasionally in other conditions. Barnes and Mann have reported experiments in which simple opening of the pericardium without other changes produced T and R-T changes similar in character to those seen after coronary artery ligation. The work of Feil, Katz, Moore, and Scott[19] emphasizes the importance of regarding these electrocardiographic changes as an indication of ischemia irrespective of the cause.

CONTROL STUDY

For purposes of comparison, electrocardiographic tracings were taken in each instance before the operation was begun, the animal being under full amytal anesthesia at the time. As a further control,

two dogs were subjected to every detail of the operative procedure except for the actual tying of the ligature.

The electrocardiograms taken before the operative procedures were instituted indicate clearly the extreme variability of the so-called

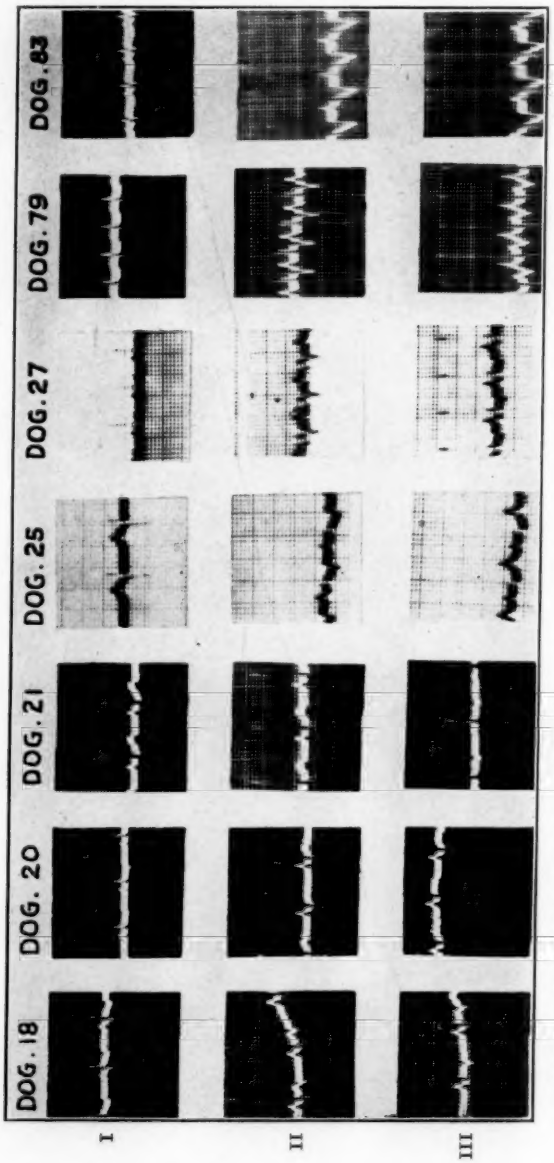

Fig. 1.—*Control* variations in T-wave. *Dog 18*, inversion of T-wave in all leads, with cove-plane type of inversion in Lead III. *Dog 20*, flattening of T-waves in Leads I and II, upright T in Lead III. *Dog 21*, upright T-wave in Leads I and II, inverted T in Lead III. *Dog 25*, flat T in Lead I, inverted, sharply pointed T in Lead II, upright T in Lead III. *Dog 27*, flat T in Lead I, diphasic T in Lead II, inverted T in Lead III. *Dog 79*, shallow inversion of T in Lead I; sharply pointed negative T in Leads II and III. *Dog 83*, flat T in Lead I, deeply negative T in Leads II and III.

"normal tracing" of the dog (Fig. 1). Of the 50 dogs in which electrocardiographic data were available, T_1 was positive in 13 dogs, isoelectric in 10, diphasic in 2, and inverted in 25. The T negativity was of variable magnitude, usually sharply pointed, and not unlike that

described as "typical of coronary occlusion." Of the 25 dogs in which T_1 was negative in the control period, T_2 was positive in 6 instances, negative in 10, and diphasic in 9, while T_3 was positive in 15 instances, diphasic in 4, and negative in 6. In only one instance was there any deviation of the S-T or RS-T segment of the electrocardiogram. In one of the two control animals no early electrocardiographic changes were noted. Nine hours after operation, however, there were slight directional changes in the T-waves, which became pronounced by the third, fourth, and fifth days, and were noted in lessened degree over a further period of three weeks. In the second control animal, slight S-T and RS-T changes were noted in the first nine hours postoperatively. Twenty-two hours after operation there were further directional changes in the T-waves, and two days later the dog was found dead.

COMMENT ON CONTROL STUDY

T-wave negativity, even of the cove-plane type in Lead I, Leads I and II, or in all three leads cannot be considered as pathognomonic of coronary occlusion. Moreover, it is evident that there is a marked variation in the normal tracing of the dog, and that the interpretation of any tracing after coronary closure is of no great value unless it is studied in comparison with a control tracing.

CHANGES FOLLOWING LIGATION OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

The changes noted consisted chiefly of (a) disturbances of rhythm and (b) changes in the direction and configuration of various components of the electrocardiogram.

Disturbances of Rhythm.—Several types of arrhythmia were frequently encountered following coronary artery ligation. A large number of dogs (15 of 50) developed ventricular fibrillation either immediately or within ten minutes following ligation. Graphic tracings of several of these instances were recorded. When ventricular fibrillation did not occur immediately, there was usually a period of normal rhythm for a variable number of hours, following which in 18 recorded instances there appeared isolated premature ectopic contractions, arising as a rule from more than one focus, usually both nodal and ventricular, rarely auricular. These did not usually make their appearance before three hours after ligation—in some instances not before 24 hours after ligation. The greatest incidence of onset was from six to eight hours following ligation, 12 of the 18 appearing at this interval. In every instance in which ectopic beats appeared, a nodal or ectopic ventricular tachycardia followed within one to two hours. At first the intervals of tachycardia were brief, consisting of not more than 6 to 8 beats, but these quickly lengthened, and being a mixture

of tachycardias resulting from stimuli arising in different foci, the rhythm was grossly irregular. Those animals which developed ectopic

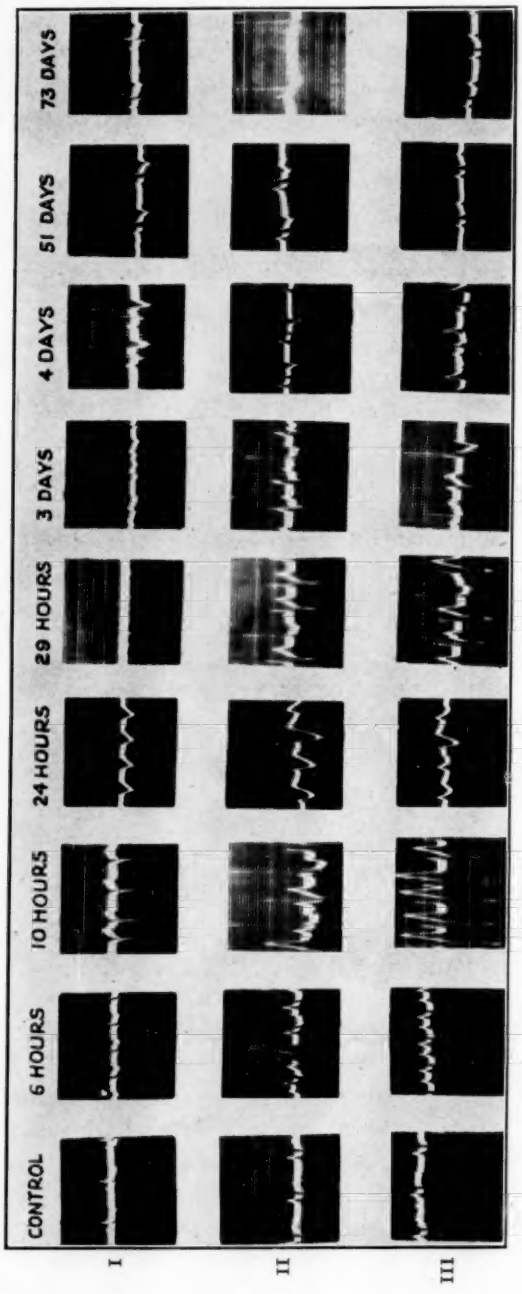

Fig. 2.—Disturbances of Rhythm—reversible sequence of rhythm changes. Isolated ventricular premature beat in Lead I, six hours following ligation. Mixture of premature beats and ectopic ventricular tachycardia ten hours after ligation. Impure ventricular flutter and ventricular tachycardia with questionable ventricular fibrillation in Leads II and III, 24 hours after ligation. Mixture of ventricular premature beats and ventricular tachycardia 29 hours after ligation. Isolated premature beats 3 days following ligation. Normal sinus mechanism 4, 51, and 73 days following ligation.

tachycardia were obviously in a terminal state, since they were found dead in their cages within twenty-four to forty-eight hours. It is quite likely that ventricular fibrillation followed these ectopic tachy-

cardias because it was possible to obtain a record showing the transition to ventricular fibrillation in several instances. In one instance the sequence of arrhythmia was reversible. There developed a sequence of premature beats, nodal and ectopic ventricular tachycardia, a brief

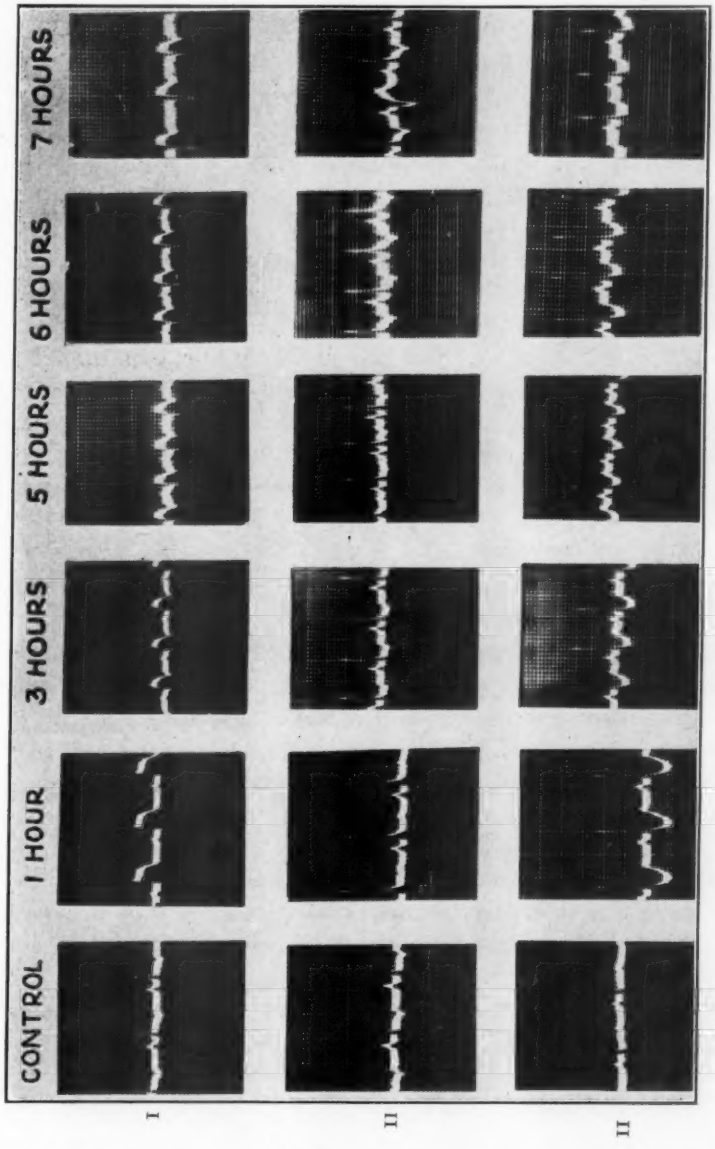

Fig. 3.—S-T Segment changes following ligation. Monophasic type of S-T wave in Leads I and III, 1 hour following ligation. Beginning of inversion of T in Lead I, appearance of negative T in Lead II and decrease of amplitude of S-T deviation in Lead III, 3 hours after ligation. High take-off in Lead I, and low take-off in Lead III, most conspicuous 1 hour after ligation, becoming progressively less prominent 3, 5, 6, and 7 hours after ligation. Typical cove-plane type of inversion of T in Lead I, 6 and 7 hours after ligation.

period of impure ventricular flutter, then ventricular tachycardia, nodal and ectopic ventricular premature beats, and finally normal rhythm (Fig. 2).

Comment on Disturbances of Rhythm.—The disturbances of rhythm incident to coronary closure are seen to follow a definite pattern.

Ventricular fibrillation is usually the terminal event in the series of rhythm changes. As a rule, the sequence of events is as follows: (1) premature beats arising singly and from various foci, usually ventricular and nodal, rarely auricular; (2) paroxysms of ectopic ventricular tachycardia, at first of short duration, later lengthening and followed by (3) ventricular flutter, usually very transient and passing almost immediately on to (4) ventricular fibrillation and death. The appearance, therefore, of isolated premature contractions following coronary artery closure is to be considered as having considerable prognostic import, presaging the possibility of the later occurrence of ectopic ventricular tachycardia, ventricular flutter, ventricular fibrillation, and death.

Changes in Direction and Configuration of T, S-T and RS-T Components.—R-T Deviation (Fig. 3): Within one hour following ligation, that is, in the acute stage of the myocardial damage, there was a deviation of the R-T or S-T segment from the isoelectric line. In Lead I in 26 of 33 dogs studied serially, the R-T segment of the curve started from the descending limb of the R-wave a variable distance above the isoelectric level. In 9 of these 26 instances the onset of origin of R-T above the isoelectric level was pronounced, varying from 3 to 6 mm., whereas in 17 instances this deviation was slight, varying from 1 to 3 mm. (1 mm. standardized to equal 1 mv.).

Where the high origin from the descending limb of the R-wave was pronounced (3 to 6 mm.) there tended to be a plateau-shaped, slightly convex elevation which then descended gradually to the isoelectric level at a point corresponding to what appeared to be the apex of a sharply pointed negative T-wave in subsequent curves. In those instances in which the origin above the isoelectric level was less pronounced (1 to 3 mm.), there was a very slight upward convexity which led immediately to a cove-plane, sharply pointed negative T-wave. In those instances in which the R-T_1 deviation was of great magnitude, the gradual descent to the isoelectric level and the apparent absence of the T-wave gave rise to a monophasic type of curve. This degree of elevation of the (R-T) segment above the isoelectric level appeared to be maximum in the first two hours after ligation, after which there was a gradual return to normal, requiring two to twenty-four hours for its completion. Definite T-waves in the monophasic type of curves were apparent before the R-T segment had completely returned to normal, and in every instance the direction of the T-wave was directly opposite to the deviation of the R-T segment. Where the R-T_1 deviation had been slight, the T-wave was negative in every instance. This corresponds to the T_1 type of curve described by Parkinson and Bedford[11] and by Barnes and Mann.[13]

In Leads II and III R-T deviations were also present, being particularly marked in Lead III, in which lead it was constantly opposite in

direction to that in Lead I. That is, where R-T arose above the isoelectric level in Lead I, there was a corresponding depression of R-T or (S-T) below the isoelectric level in Lead III. In the 7 instances in which R-T_1 deviations were not present, there was a noticeable depression of the R-T (S-T) level in Leads II and III, comparable, though in lesser degree, to that seen where R-T_1 changes were definitely present.

T-Wave Changes.—In the acute stage of the myocardial damage, as indicated above, the T-wave changes are essentially constant, being opposite in direction to the R-T or S-T deviation, and conforming to the T_1 type of Barnes and Mann[13] and of Parkinson and Bedford.[11] Essentially, they are inverted in Lead I and directed upward in Lead III. They tend, as a rule, to be sharply pointed, of the cove-plane type described by Oppenheimer and Pardee. Beginning about twenty-seven hours after ligation, the most conspicuous feature is the variability of the size, shape, and direction of the T-waves from day to day, following no fixed pattern, and showing changes over a period as long as seventy-three days. As a rule, the changes are in the direction of the normal, being first noticed in Leads II and III but often stopping short in Lead I so that T_1 may remain inverted or flattened. These facts indicate quite clearly that it is the change from day to day which is the feature of coronary closure rather than a characteristic coronary type of T-wave. Early there was frequently a conspicuous increase in the amplitude of the T-wave. As a rule, it required from one to four weeks before the T-waves assumed a normal appearance, but even after this period in some dogs T-wave changes persisted, particularly in Lead I and continued until the death of the animal.

OTHER ELECTROCARDIOGRAPHIC CHANGES

QRS Waves.—Contrary to clinical coronary occlusion, in which widening and notching of the initial ventricular deflection is commonly met with, this condition was rarely encountered in experimental occlusion in dogs. Low voltage of the QRS waves in Lead I was a noticeable feature in more than half of the experiments. It occurred either within the first three hours following infarction or not until about a week following the coronary occlusion. Rarely there occurred a subsequent increase in voltage, but as a rule, when once present, it persisted for the remainder of the experiment. It would seem, therefore, that a previous diffuse myocardial fibrosis is not necessary for low voltage of QRS and that coronary occlusion with myocardial infarction may, in itself, be sufficient to bring about this abnormality. Left or right axis deviation, bundle-branch block, accentuation of the Q-wave in Lead III were rarely encountered.

EFFECTS OF RELEASE OF LIGATURE

In 8 dogs the coronary vessels were ligated for varying periods of time up to eight hours. At the end of different intervals the ligatures were removed and the animals killed two hours afterward. The most conspicuous result of releasing the ligature was the rapid onset of marked arrhythmia, premature beats, ventricular tachycardia, and in one instance ventricular fibrillation. It is interesting to note that, whereas no demonstrable characteristic alteration was observed in the myocardium of animals whose coronary vessels remained ligated for less than one hour, in this second group in which the ligature was released, striking gross and microscopic changes were present in every case except in one instance in which the vessels were ligated for only one-half hour.

CORRELATIVE DISCUSSION

In correlating the electrocardiographic changes with the thermometric, anatomical, and chemical changes as reported in previous papers, several features are of interest. The immediate fall of surface temperature in the ischemic zone, the marked anatomical changes as indicated in these experiments in which the ligatures were released at varying periods up to eight hours after ligation, the immediate increase up to 100 to 200 per cent of lactic acid, with a similar decrease in glycogen content over that of the control zone—all these findings indicate a profound alteration in the ischemic zone. It is not at all surprising, then, that this injured zone profoundly and regularly alters the normal action current of the heart in a conspicuous and characteristic fashion, immediately after coronary closure.

GENERAL DISCUSSION

It is apparent that in dogs there is a marked normal variability of the T-waves, T_1 negativity being chiefly encountered, but negativity of T being found also in Leads II and III. It is further apparent that the so-called characteristic coronary type of T-wave (Pardee) or cove-plane type of T-wave (Oppenheimer) may also be encountered during experimental procedures in dogs in the absence of coronary ligation and with no evident myocardial injury. Deductions derived from the appearance of the T-waves of dogs are therefore of little value unless control tracings are available for comparison.

From the experimental results presented, it would appear that the deviations of the R-T and S-T segments are the most conspicuous and most frequent electrocardiographic evidences of recent focal myocardial injury. The deviation of this segment above the isoelectric level in Lead I and a corresponding depression below this level in Lead III are in agreement with the statement of Parkinson and Bedford,[11] Barnes and Whitten,[12] and Barnes and Mann,[13] that occlusion of

the anterior descending branch of the left coronary artery with focal injury chiefly at the apical portion of the left ventricle gives rise to a characteristic T_1 type of curve. In the normal heart of the dog the current of injury supplied by this area of focal necrosis is of relatively brief duration as evidenced by the transient nature of the R-T deviation.

An early marked increase in amplitude of the T-waves, directional changes in the T-waves, characteristically opposed to that of the R-T or S-T deviation, a deep, cove-shaped negativity, particularly in Lead I, and more particularly the successive changes from day to day and from week to week up to the longest period of observation (73 days) may be considered as evidences of reparative processes in the affected myocardial area. Special emphasis must be placed upon the successive changes and the importance of serial study rather than on the appearance of an isolated T-wave. The frequent occurrence of low voltage of the initial deflection in Lead I deserves particular comment in relation to coronary occlusion. Its frequent appearance immediately following occlusion indicates clearly that a previous diffuse fibrosis is not essential for its presence and that coronary occlusion alone may be a factor in its production.

The sequential type of rhythm disturbance following coronary occlusion merits special emphasis. It is obvious that ventricular fibrillation is usually the cause of death in the experimental animal and further that it frequently develops within a few minutes after the artery is occluded. However, in many instances there is an appreciable time interval, usually hours, before ventricular fibrillation sets in, and the probability of its appearance is indicated first by the appearance of isolated premature contractions arising chiefly in the ventricle or nodal tissue, later by ectopic tachycardia, usually ventricular, and finally a brief period of ventricular flutter. The appearance of any of these arrhythmias is therefore of considerable prognostic import.

SUMMARY

1. In 50 dogs under full amytal anesthesia and before operative procedures, control electrocardiograms indicated marked normal variations of the T-waves. T_1 was positive in 13 instances, isoelectric in 10, diphasic in 2, and inverted in 25. T_1 negativity was usually accompanied by T_2 and T_3 positivity, but in several instances T_2 and sometimes T_2 and T_3 were also negative. Of the 25 dogs in which T_1 was negative, T_2 was positive in 6 instances, negative in 10, and diphasic in 9. T_3 was positive in 15 instances, diphasic in 4, and negative in 6. T_1 negativity was of variable magnitude, not infrequently sharply pointed and not unlike that described as typical of coronary occlusion. In only one instance was there any deviation of the S-T or RS-T segment of the electrocardiogram.

2. Occlusion of the anterior descending branch of the left coronary artery is attended with characteristic electrocardiographic changes. In 26 of 33 dogs serially studied, deviations of the R-T segment were present, being pronounced in 9 instances and slight in 17 instances. These deviations are most conspicuous in the first two hours following ligation, that is, in the acute stage of myocardial infarction. These changes with associated negativity of the T-wave in Lead I are in accordance with the T_1 type of change as described by Parkinson and Bedford, Barnes and Whitten, and Barnes and Mann.

3. Increased amplitude of T-waves, sharp negativity of the T-waves, particularly in Lead I, and successive directional and amplitudinal changes in the serial of electrocardiograms persisting as long as seventy-three days following ligation were noted. Low voltage of the initial ventricular deflection in Lead I was frequently encountered.

4. Characteristic changes of rhythm were noted following coronary occlusion. Fifteen dogs developed ventricular fibrillation either immediately or within ten minutes following ligation. When ventricular fibrillation did not occur immediately, there was usually a period of normal rhythm for a variable number of hours, following which in eighteen recorded instances, there appeared premature contractions, usually both nodal and ventricular, rarely auricular. This was followed by nodal or ventricular tachycardia and later ventricular flutter, ventricular fibrillation, and death of the animal.

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PRACTICAL APPLICATION OF THE METABOLIC EXERCISE TOLERANCE TEST TO THE TREATMENT OF HEART DISEASE*†

BASIL BLUMENTHAL, M.D.
CHICAGO, ILL.

KATZ, Soskin and their associates[1] have developed a feasible laboratory procedure for estimating, in an objective manner, the functional status of patients with heart disease. This test is based on the excess oxygen consumption accompanying the performance of a standard exercise. When a large group of ambulatory patients were subjected to this test, the functional capacity of the heart as judged from the excess oxygen consumption was found roughly to parallel the clinical assay of the cardiac status. However, subsequent testing by Dr. H. Strauss[2] of a group of some fourteen ambulatory patients with coronary sclerosis and angina pectoris yielded exercise tolerances within the normal range. It seemed evident that the functional capacity of the heart was not the only factor determining the excess oxygen consumption, and further studies were deemed advisable.

In the present study, three patients with congestive heart failure of a degree which demanded rest in bed were tested during their hospital stay.

REPORT OF CASES

CASE 1.—A pregnant woman with severe thyrotoxicosis, having dyspnea, palpitation, and tachycardia, was tested sixty days after admission with complete bed rest and showed 9.5 c.c. excess oxygen per kilogram meter of work per square meter of body surface.

CASE 2.—A patient with diabetes mellitus, arteriosclerotic heart disease and congestive heart failure had four tests during her stay in the hospital. These were run 1, 4, 9, and 14 days, respectively, after admission. The results ranged between 9.9 and 5.3 c.c. excess oxygen per kilogram meter of work per square meter of body surface, the individual values being 5.3, 7.3, 9.1, and 9.9 c.c. excess oxygen per kilogram meter of work per square meter of body surface.

These values were within or close to the normal range of excess oxygen consumption found previously with this test, viz., 2.2 to 7.5 c.c. excess oxygen per kilogram meter of work per square meter of body surface. The question, therefore, arose as to whether the bed rest which these patients had had prior to their tests could have been responsible for their relatively good exercise tolerance. Evidence suggesting that this was so was obtained in an extremely cooperative patient during her recovery from congestive heart failure which was complicated by a temporary return of congestive failure.

CASE 3.—Mrs. R. M., aged thirty-eight years, was admitted on Nov. 16, 1934, to the Michael Reese Hospital on Dr. Hamburger's service. She was slightly cyanotic,

*From the Heart Station and the Max Pam Unit of the Michael Reese Hospital.
†Aided by the F. K. Babson and Max Pam Funds.

extremely dyspneic, and orthopneic. Signs of fluid in the right pleural cavity were present. Râles were heard over the left lung base. The neck veins were pulsating; the liver was down three fingerbreadths below the costal margin and was tender. The heart was enlarged to the right and left, both systolic and diastolic murmurs were heard over the apex. Auricular fibrillation was evident; the average ventricular rate was 94 beats per minute; and the pulse deficit was 8.

The patient gave a history of scarlatinal infection in childhood with no complications. She had no history of rheumatic fever or chorea. Five years before admission she had experienced sudden severe pains in the chest and had a hemoptysis which forced her to go to the hospital where she remained for five weeks. Since then, she had had attacks of palpitation, with increasing ankle edema, orthopnea, and dyspnea.

She was put to bed on admission and received digitalis leaf, 1 grain daily. On November 17 her basal metabolic rate was +31 per cent. On November 18 her dyspnea was less marked. Her exercise tolerance test on this date was 31.1 c.c. excess oxygen per kilogram meter per square meter. The arm-to-tongue circulation time was 26 seconds.

On November 21 she was much improved clinically. Basal metabolic rate was +18 per cent; ventricular rate, 84; pulse deficit, 12; arm-to-tongue circulation time, 25.5 seconds. Exercise tolerance was 16.2 c.c. excess oxygen per kilogram meter per square meter.

On November 22 patient was allowed up in a wheel chair for one hour each afternoon.

Three days later clinical improvement continued. Exercise tolerance was 16.7 c.c. excess oxygen per kilogram meter per square meter.

On November 27 exercise tolerance was 18.6 c.c. excess oxygen per kilogram meter per square meter; ventricular rate, 76 with no pulse deficit; the basal metabolic rate was +15 per cent.

On November 28 patient developed anorexia, was nauseated, vomited, and had diarrhea. The fibrillation of the auricles was still present, the ventricular rate was 64 with no pulse deficit. The patient was put back to bed.

The next day the patient was very apprehensive. The ventricular rate was 80 and the pulse deficit, 6. The exercise tolerance was 35.9 c.c. excess oxygen per kilogram meter per square meter.

On December 2, after four days of bed rest, the patient was clinically better, and subjective symptoms were no longer present. She was more quiet and composed. Ventricular rate was 56; pulse deficit, 6. Exercise tolerance was 24.2 c.c. excess oxygen per kilogram meter per square meter.

On December 5 the patient was much improved and was ready to go home. Exercise was 14.9 c.c. excess oxygen per kilogram meter per square meter.

The next day the physical examination showed auricular fibrillation, and an explosive systolic murmur over the apex was present with P_2 accentuated. Liver dullness extended two fingerbreadths below the costal margin. The liver was not tender. Occasional moist râles were heard at the base of the lungs.

The patient went home, rested a number of hours daily, and continued to take digitalis. She was readmitted two months later for study regarding a total thyroidectomy. At that time there were no signs of congestive failure. She still had auricular fibrillation with an average ventricular rate at the apex of 80. During this stay at the hospital, her exercise tolerance was tested (Feb. 18, 1935) and gave a value of 15.5 c.c. excess oxygen per kilogram meter per square meter.

COMMENT

The changes in exercise tolerance of this patient are plotted in Fig. 1. While this patient always showed an exercise tolerance definitely outside normal limits, her low values were not far outside the normal range. The observations in this patient are illuminating in showing how labile the exercise tolerance test can be and how closely the exercise tolerance follows the clinical course. In fact, it seems that the exercise tolerance returned toward its stable level before other evidences of clinical improvement were apparent.

This experience suggests that the metabolic exercise tolerance test is not so much a measure of the functional capacity of the heart as it is

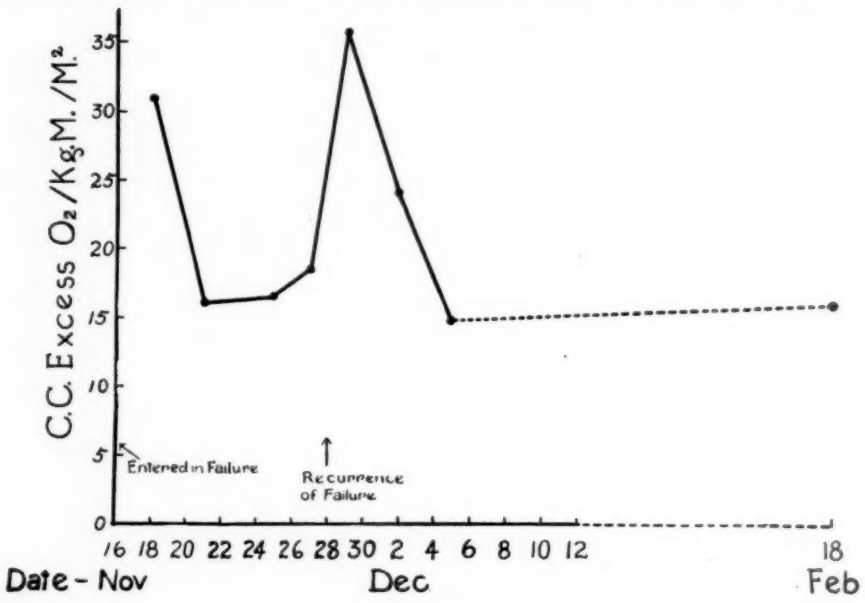

Fig. 1.

an index of how close the patient is to the *limit* of functional capacity at the time of the test. In other words, it is a measure of the functional cardiac reserve rather than of the functional cardiac capacity, if by reserve is meant the difference between the total strain the heart can withstand (its functional capacity) and the strain under which it is working. Thus, the strain upon the heart cannot be ignored in evaluating the significance of the test. A patient with a low functional capacity may show a normal exercise tolerance if his heart has been spared from strain by proper and continued bed rest. On the other hand, a patient with a relatively good functional capacity may show an abnormal exercise tolerance if his heart has been put to undue and continued physical (and/or emotional) strain. In the same patient, no change in exercise tolerance is to be expected if the strain on the heart is reduced

proportionately to the reduction in its functional capacity, nor will the exercise tolerance vary if the strain on the heart is increased proportionately to the increase in its functional capacity.

According to this conception, the test when applied to ambulatory patients has practical utility since it can give the physician information as to how well adjusted the patient's activity is to his functional cardiac capacity. The test when properly interpreted could help the clinician in prescribing the regimen best suited for his individual cardiac patients. A return of the metabolic exercise tolerance to the normal range would justify the trial of an increased work schedule. Especially significant would be an abnormally poor tolerance which would indicate clearly the immediate need of reducing the amount of activity which the patient is allowed.

I wish to acknowledge my indebtedness to Dr. L. N. Katz and Dr. S. Soskin, at whose suggestion this study was made, for guidance and aid in interpreting results.

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Department of Clinical Reports

GONOCOCCUS AORTITIS, WITH MULTILOCULAR ANEURYSM AND CONGENITALLY BICUSPID AORTIC VALVE

CASE REPORT*

E. STERLING NICHOL, M.D., AND MAX DOBRIN, M.D.
MIAMI, FLA.

INSTANCES of infection of the aorta by the gonococcus are quite rare, only nine cases being found in a recent search of the literature by Aschner.[1] The present case is reported because of the unique combination of a multilocular aneurysm of the aorta with acute vegetative gonococcus aortitis and congenitally bicuspid aortic valve with acute vegetative gonococcus endocarditis.

CLINICAL NOTES

The patient (J. E. T.), a white male, fifty-seven years of age, was admitted July 19, 1934, to the Jackson Memorial Hospital, Miami. For three months prior to admission he had suffered with night sweats, weakness, and loss of appetite. He also complained of joint pains, slight swelling of the ankles and occasional nausea and vomiting. Later, nocturia and pain on micturition were noted. There had been a weight loss of 30 pounds (13.6 kg).

Past History.—Five months before admission to the hospital he had gonorrhea, for which he had treated himself with injections of argyrol. Otherwise his previous health had been good, except for the usual childhood diseases.

Examination.—On admission he appeared quite ill, with temperature 102.4° F., pulse, 108; and respiration, 24. There was slight impairment of the breath sounds over the right chest posteriorly. The heart was within normal limits on percussion; a soft systolic murmur was audible at the aortic valve area, but no thrill was palpable; the blood pressure was 100/70. Otherwise the physical findings were essentially normal.

Laboratory Data.—Urinalysis: specific gravity 1.011, slight trace of albumin, no acetone bodies; sediment contained occasional leucocytes, erythrocytes and granular casts. Hemogram: erythrocytes, 3,440,000; hemoglobin, 65 per cent; leucocytes, 18,750, with 85 per cent polymorphonuclears, 12 per cent lymphocytes, 2 per cent basophiles, and 1 mononuclear. The blood Kahn, Widal and agglutination tests for undulant fever were negative. The blood nonprotein nitrogen was 42 mg., the creatinin 1.5 mg. per 100 c.c. Blood culture taken Aug. 29, 1934, showed no growth after twelve days' incubation, but cultures made Oct. 24, 1934 and Nov. 10, 1934, both showed gram-positive biscuit-shaped diplococci. The complement fixation test for gonococci was reported positive on Nov. 14, 1934, by the United States Public Health Service Laboratory, Washington, D. C.

Diagnosis and Course.—In view of the evidence of a serious type of infection and the absence of other findings, the tentative diagnosis of gonococcemia seemed warranted because of the recent gonorrheal urethritis. However, no definite diag-

*From the Jackson Memorial Hospital, Miami.

nosis was reached at first, owing to the early negative blood culture, the absence of an enlarged spleen and the absence of petechiae. The fever was continuous, intermittent and remittent, the fluctuations being from 96° to 102° F., or even 105° F. on some occasions. The patient became weaker, the anemia more marked, so that by November 10 the hemoglobin was down to 32 per cent in spite of his having received three transfusions. The recovery of an organism from the blood morphologically similar to the gonococcus on two occasions later on, and the appearance of petechiae and the presence of erythrocytes in the urine finally determined the diagnosis of gonococcemia beyond reasonable doubt, although more than three months after admission to the hospital.

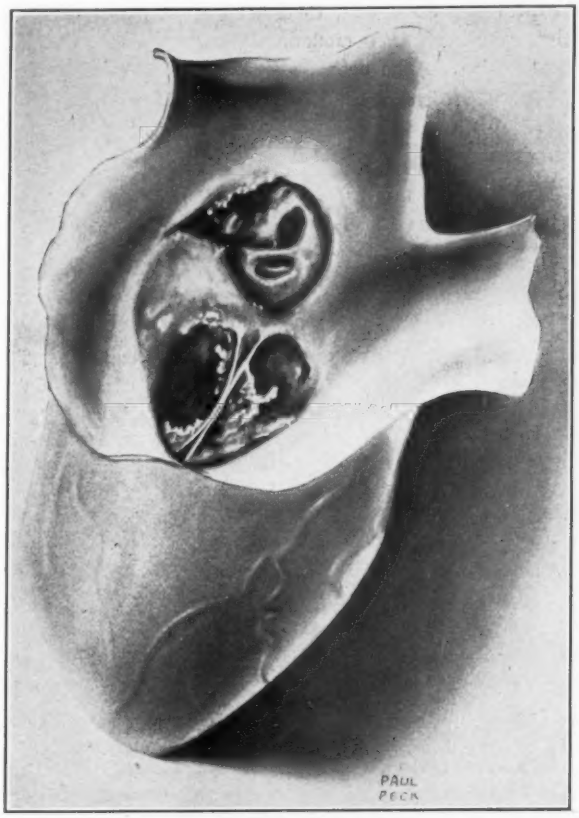

Fig. 1.—Drawing of heart after opening aorta displaying multilocular aneurysm above, and bicuspid aortic valve below.

The constancy of the systolic aortic murmur and the advent of a rather faint diastolic aortic murmur were the basis for the diagnosis of acute gonorrheal endocarditis, although on November 10 one of us (E. S. N.) made the following consultation note: "Systolic murmur of low intensity over aortic area. Very faint diastolic murmur (aortic). No cardiac enlargement. Pulse 72. Hard to visualize endocarditis in this patient unless primarily mural rather than valvular."

One of us (M. D.) mentioned gonococcus aortitis as a possible diagnosis, basing this thought on the presence of an infectious nidus, which probably was not a valvulitis because of the absence of cardiac hypertrophy and auscultatory findings pointing to the lack of destructive valvular lesion, but considered the likelihood of such a condition rather remote.

On Nov. 16, 1934, the patient became stuporous, Cheyne-Stokes respiration developed, and he expired, nearly four months after entering the hospital, and seven months after the initial symptoms were noted.

CONDENSED REPORT OF NECROPSY

Dr. I. Youmans examined the body after embalming. The skin showed small hemorrhagic petechiae scattered over the abdomen, hands, and knees; there was some edema of the legs. Bilateral pleural adhesions of moderate degree and hypostatic congestion of both lung bases were noted. The spleen was somewhat enlarged and showed one small infarct. The capsules of both kidneys stripped easily, and, though no gross infarcts were found, there were minute hemorrhagic areas in the cortex. The liver was enlarged moderately and appeared to have undergone chronic passive congestion. (The heart will be described below.)

Microscopic study of sections from the kidneys showed acute and chronic inflammatory changes, with some hemorrhagic areas and minute abscesses in the parenchyma. Sections from the liver showed hyperemia and cirrhotic changes, and general cell invasion and accumulations of cells approaching small abscess formation.

The Heart and Aorta

Because structural changes of questionable etiology were found in the aorta the specimen was sent for study to Dr. Clarence E. de la Chapelle, whose gross and microscopic findings are summarized below:

"The *heart* and *aortic arch* weigh 282 grams (after fixation). The pericardium is smooth and glistening. The chambers and valves of the right side of the heart are normal in all respects, and the pulmonary artery shows nothing remarkable. On opening the left side of the heart, concentric hypertophy of the left ventricle is apparent, the ventricular chamber being quite small, while the wall measures 22 mm. in thickness at the base and 20 mm. at the apex. The mitral valve is slightly and irregularly sclerosed along its margin, but is otherwise normal and free from vegetations. The chordae tendineae are normal as are also the papillary muscles. The left auricle presents no abnormal features.

"The *aortic valve* is congenitally bicuspid (Fig. 1.), with some sclerosis and calcification of its margin, and some calcification of what is apparently the posterior cusp. The commissure situated posteriorly is widened (5 mm.), the anterior one, however, is normal. The ostium of the left coronary artery, situated in the posterior portion of the sinus of Valsalva of the "posterior" cusp, is large, while the right coronary artery is seen to have a double (congenital) ostium being formed by two small openings about 1 to 2 mm. in diameter located in the anterior portion of the same sinus. The course and appearance of both coronary arteries are normal. The sinus of Valsalva of the other aortic cusp is dilated into an aneurysmal pouch, the interior of which is relatively smooth.

"An aneurysm with a diameter of 28 mm. and a depth of 15 mm. is present in the supravalvular portion of the aorta, its lower border being 8 mm. above the posterior commissure of the aortic valve. The margin of this aneurysm is smooth, except on the upper border which is ragged and torn, and just beneath the margin fresh vegetative material fills up about one-third of the floor, while the remainder of the floor consists of multiple loculations smooth and free from vegetations, grouped in a rather bizarre fashion, giving a honeycomb appearance.

"Upon cross-sectioning the aneurysm, about half of its wall is seen to be made up by the superior vena cava, the rest by the right branch of the pulmonary artery as it crosses beneath the arch of the aorta. Some of the loculations are thus revealed as smooth small pouches varying in size from a few millimeters to 1 centi-

meter. The rear wall of the aneurysm seems necrotic and a small hemorrhagic infiltration is noted, seen as a discolorated area through the endothelium of the superior vena cava. The remainder of the aorta is smooth, with here and there an atheromatous plaque. The supravalvular portion is dilated measuring 8.2 cm. in circumference just above the ring of the aortic valve, but the isthmus portion is of normal size, measuring 5.6 cm. in circumference."

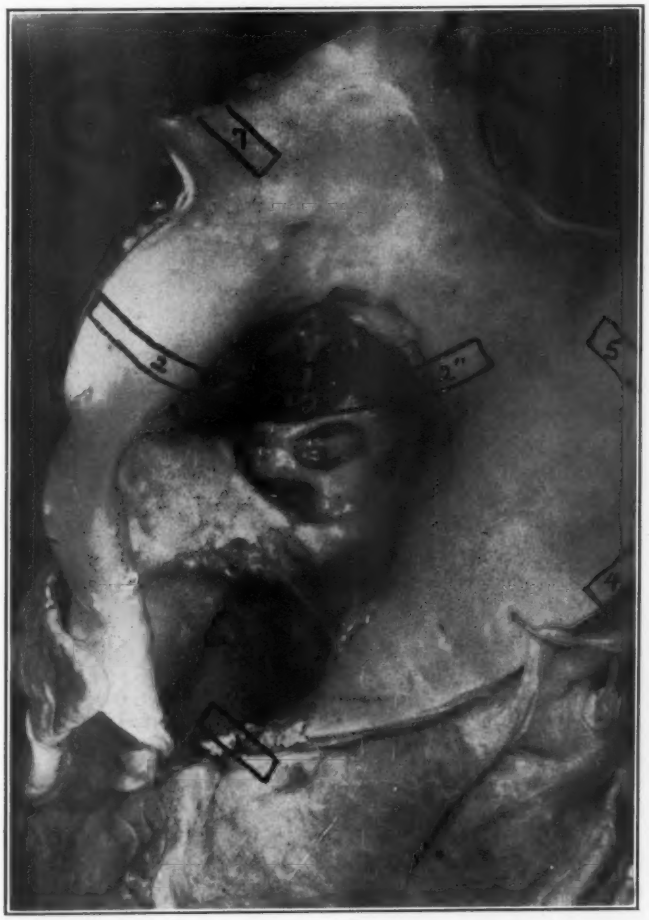

Fig. 2.—Locations from which sections were cut: 1, aortic valve; 2, 2', and 2'', aneurysm and adjacent aorta; 3, floor of aneurysm; 4, 5, 6, and 7, aorta.

Microscopic Findings

"The sites of the most important sections studied are shown in Fig. 2. All sections were stained with hematoxylin and eosin unless otherwise indicated in the descriptions.

Aortic Valve (Section *1*).—This valve is thickened by hyalinized fibrous tissue and a small area of calcification is visible. Superficially on both the ventricular and aortic aspects of the cusps there is a suppurative inflammatory lesion, appearing as a vegetative process on the inferior aspect, made up of thrombus material with innumerable polymorphonuclear leucocytes, a few lymphocytes, and some clusters of débris and bacteria: chiefly gram-negative cocci, a few gram-negative intracell-

ular diplococci, and scattered gram-positive organisms. (Goodpasture, Brown and Brenn stains.) This acute inflammatory response has apparently involved only the superficial substance of the valve, and even at the base of the vegetation there is no striking cellular response visible, although in the muscular portion (septum of the left ventricle) adjacent to the aortic ring, the leucocytic response is quite intense, and scattered areas of old fibrosis are also visible here.

Aneurysm and Adjacent Aorta (Sections *2*, *2'*, and *2"*).—The aorta as seen in Section *2* represents a variable picture as the aneurysmal pouch is approached, ranging from cloudy swelling, vacuolization, fatty changes, and nuclear degeneration to complete loss of nuclei and muscle striations. The intima, subintima, and adventitia are involved by a diffuse suppurative process, mostly polymorphonuclear in a nature, but also including some lymphocytes and plasma cells. The vasa vasorum have undergone thickening, but there is no perivascular cellular infiltration to suggest syphilis. Innumerable thin-walled vessels are present in the thin layer

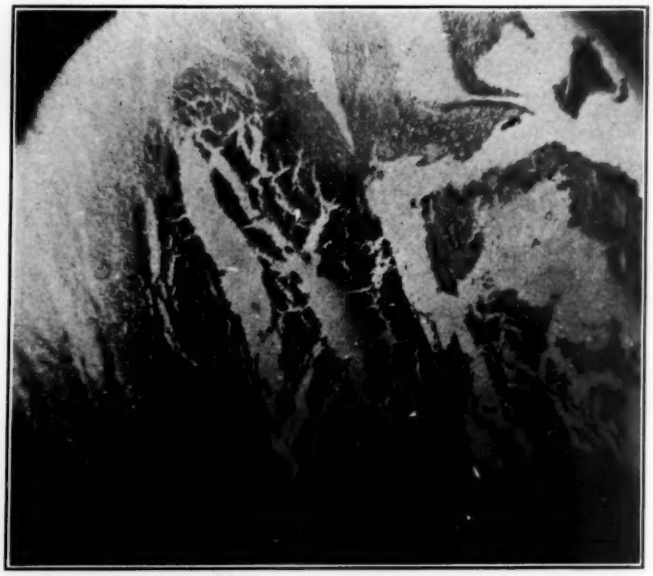

Fig. 3.—Low power photomicrograph of section 2' through floor of the aneurysm.

of tissue which may have been the adventitia and which forms most of the floor of the aneurysm in this section. The pouch of the aneurysm is filled with loose vegetative thrombotic material, including polymorphonuclear leucocytes, lymphocytes, fibrinous débris—a distinct suppurative lesion. A bacterial stain reveals scattered diplococci in this area.

"In Section *2'* (Fig. 3) the underlying wall of the aorta has disappeared and the suppuration extends to and even infiltrates the wall of the superior vena cava, producing a panphlebitis including endophlebitis. The latter presents itself as a small vegetative nodule raised above the endothelial surface and made up mainly of leucocytes and occasional plasma cells. Considerable hemorrhage into the suppurative area and engorgement of the thin-walled blood vessels in the poorly organized fibrous tissue is readily visible. The limiting border of one of the large loculations is seen to consist of fibrous tissue in part hyalinized, while adherent to the inner surface of the smaller sac is a wide thrombus composed of débris and bacteria. This area stained with Weigert elastic stain shows destruction and interruption with thinning of the elastic layer of that part of the wall of the superior

vena cava adjacent to the floor of the aneurysm. No elastic fibers are seen in either the septum or wall of the loculation.

"A small part of the right branch of the pulmonary artery is visible in Section *2"* immediately adjacent to the thin adventitia of the aorta which appears, still forming the floor of the aneurysm and the smaller pouches. Beyond this point under the overhanging margin of the torn edge of the aorta, the suppurative process is again seen, consisting mainly of leucocytes, erythrocytes, fibrinous débris and bacteria. (Using the Brown and Brenn stain a few gram-negative intracellular cocci are seen scattered about in this suppurative process.) The torn and ulcerated margin of the aorta is inverted in a suppurative vegetative thrombus beyond which an intense inflammatory lesion involves the intima and subintima of the aorta, diminishing in intensity distally. At the point of rupture the media shows marked degeneration with nuclear destruction, swelling and necrosis of the fibers and intense infiltration by leucocytes. A few strands of broken elastic fibers remain scattered throughout and near the mesial portion of the aorta the adventitia is markedly thickened.

"In another section through the floor of the aneurysm (Section *3*) a loculation is completely visible, the structure of which is similar to the one just described, the wall consisting of old irregularly distributed connective tissue which has undergone hyalinization at some points. No elastic fibers are found in the wall on using Weigert's elastic stain.

"Sections of the aorta (*4, 5, 7,* and *7,*) 2 to 4 cm. distant from the aneurysm in various directions show variable degrees of atherosclerotic changes in the intima and subintima, with here and there mild intimal cellular response. The media presents cloudy swelling with necrotic nuclei, swollen muscle fibers (many of which have lost their striations), and edema. Some fatty metamorphosis of the muscle fibers of the media is shown with sudan III stain. In some areas there is slight focal cell infiltration of the media consisting of lymphocytes and plasma cells. The Weigert elastic stain shows broken, swollen and granular appearing elastic fibers in these sections. The adventitia here is essentially normal.

"*Other Structures.*—The *mitral valve* shows slight sclerosis and on the auricular surface a mild superficial endocardial lesion extends from the midportion to the tip, made up of a mixture of lymphocytes, fibroblasts, and endothelial cells. No vegetative or thrombotic formation or fibrinoid change is noted, nor are any bacteria seen in this area. The *pulmonic* and *tricuspid valves* are normal in structure. The pericardium is essentially normal. The *left auricle* shows slight sclerosis of the endocardium in some areas, and some cloudy swelling and fragmentation of the muscle. Some sections of the *left ventricle* show degenerative changes in the muscle fibers with swelling and loss of nuclei and striations. Similar changes are visible in the papillary muscles. In other sections the left ventricle shows only irrelevant findings, and the same is true of sections of the right auricle and right ventricle. The left coronary artery shows a slightly irregular intimal thickening by sclerosis and a mild local mononuclear response at one site. Its media and adventitia are normal. The right coronary artery appears normal."

ANATOMICOPATHOLOGICAL DIAGNOSIS

Multilocular aneurysm of the ascending aorta with acute vegetative (gonococcus) aortitis. Acute suppurative aortitis. Parenchymatous degeneration of the aorta. Aneurysm of the sinus of Valsalva. Bicuspid aortic valve (congenital) with acute vegetative (gonococcus) endocarditis. Sclerosis and nodular calcification of the aortic valve with stenosis. Double coronary ostium (congenital) of right coronary

artery. Hypertrophy (concentric) of the left ventricle. Acute focal suppurative myocarditis. Focal fibrosis and parenchymatous degeneration of the myocardium. Sclerosis of the mitral valve with early superficial endocarditis. Pleural adhesions. Noninflammatory edema of the lungs. Infarction of spleen. Glomerulonephritis. Chronic passive congestion of liver.

COMMENT

The congenital origin of the bicuspid aortic valve is indicated by the finding of only two cusps, without a raphe,* although serial sections through the valve were not made to establish further the congenital origin of the anomaly. The sclerosis and calcification of this valve may have come from attrition, for the tendency of malformed congenital segments to undergo insidious sclerosis, thickening, and calcification has been emphasized by Abbott.[2] On the other hand, the sclerotic changes in the valve may have resulted from a previous inflammation, possibly bacterial, which involved the valve.

The age of the changes noted in the aorta on microscopic examination indicates that an aneurysm existed for some time prior to the recent and terminal invasion by the gonococcus, *but the actual origin of the aneurysm cannot be stated with certainty.* Dr. de la Chappelle[3] held the opinion, in view of his microscopic findings, that the aneurysm, at least the multilocular formation, was postinflammatory in origin, and pointed out that the absence of elastic fibers in the septums of the loculations also speaks against a congenital origin. It is conceivable, even if not likely, that this individual may have had an infection involving the aorta (as well as the aortic valve as noted above) at some time in his life, producing these changes, although there was no such significant previous illness related by the patient.

Abbott[4] has pointed out that a bicuspid aortic valve is frequently associated with a congenital thinning of the aortic wall, predisposing to the formation of an aneurysm. This author[5] after examining our specimen and sections felt that the main aneurysm was primarily due to a congenital thinning of the right posterior wall of the aorta, the saccular aneurysmal bulging following, the loculi possibly developing as secondary sacculations. However, the absence of elastic tissue in the walls of the loculi was conceded undoubtedly to favor a very early inflammatory origin as far as the *secondary* sacculations were concerned.

That the present involvement of the aneurysmal pouch and aorta, in general, was by direct invasion rather than through the vasa vasorum is suggested by the marked inflammatory changes localized in the intima and the subintima, which areas are supplied by the circulating blood, not by the vasa vasorum.[3] The parenchymatous degenerative changes in the media were probably of toxic origin secondary to the gonococcus, as were the changes in the myocardium.

*Dr. Abbott noted a possible rudimentary raphe between the right and left anterior sinuses behind the composite cusp. Lack of technical facilities did not permit us to make further study of the point after the method of Lewis and Errant recently emphasized by Bishop and Trubek.

NOTE: Our thanks are tendered Dr. Clarence E. de la Chapelle for his kindness in making a detailed study of the specimen and sections and to Dr. Maud E. Abbott for her helpful suggestions.

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A CASE OF PULMONARY EMBOLISM SIMULATING CORONARY THROMBOSIS IN A YOUNG MAN AGED THIRTY-THREE YEARS*

J. Beach Hazard, M.D., and Robert Sterling Palmer, M.D.
Boston, Mass.

REPORT OF CASE

A WHITE, native American business man, thirty-three years old, complained of gradual onset of dyspnea on exertion which was first noted three weeks previously while mowing his lawn. There was slight cough, without hemoptysis, noted especially when lying flat. The dyspnea was not paroxysmal, and there was no wheezing. He had passed a life insurance examination six months previously. His blood pressure was said to have been low one year before. There was no pain, no heart consciousness, no palpitation.

Careful review of the bodily systems revealed nothing.

His hygienic habits were not remarkable. He had exercised less in the past year but had kept his weight down by dietary restriction. His diet was unusual in that he was very fond of eggs. His business had occasioned nervous strain. His sleep had been somewhat restless for two months.

One year before, the patient had suffered an attack of herpes zoster followed by a small abscess of the abdominal wall under the left costal margin which healed uneventfully. Otherwise the past history was negative.

The family history was negative except that a brother had diabetes.

Physical examination showed a slightly obese young man, quite dyspneic and coughing slightly on the slightest exertion. The left border of the heart was 8 cm. to the left of the midsternal line; the midclavicular line was 7.5 cm. The rate was 100, the rhythm regular. A questionable gallop rhythm was noted. The blood pressure was 110 systolic and 95 diastolic. The chest was clear and resonant. Expansion of the right costal margin appeared slightly less than the left. Examination of the abdomen and extremities was negative.

The hemoglobin was 100 (Talqvist), 128 and 109 (Sahli), the red blood cells numbered 6.2 and 5.4 million per cubic millimeter, the white blood cells 17,000 per cubic millimeter.

The electrocardiogram showed sinus tachycardia, rate 120, late inversion of T_2 and T_3, a small Q_4 and an upright T_4 (Fig. 1*A*).

A six-foot film of the heart showed prominence in the region of the left ventricle, but the measurements were within normal limits. There was some density of the hilus shadows thought to be due to enlarged pulmonary vessels. There was a small patch of hazy density in the right midchest just outside the hilus region consistent with consolidation or a small amount of interlobar fluid.

The sputum was negative. There was a negative Neufeld reaction to pneumococcus Types I, II, and III.

Summary.—A young male adult came to the office complaining of progressive dyspnea of three weeks' duration, was obviously short of breath, showed a rapid slightly large heart with a suggestive gallop rhythm, a slightly diminished expansion of the right chest. Examination of the blood revealed a leucocytosis and a slight polycythemia. The electrocardiogram was thought consistent with coronary occlusion and

*From the Faulkner Hospital and Department of Pathology of Tufts College Medical School, Boston, Mass.

was considered comparable to that of pulmonary embolism. The absence of any apparent origin for the latter and the gradual onset seemed against such a diagnosis, while the age of the patient and the absence of pain weighed against the former diagnosis. Also considered were primary pulmonary arteriosclerosis and pulmonary neoplasm. On the whole, coronary sclerosis with question of occlusion was thought most likely.

The patient was hospitalized. He gradually grew worse, ran a low fever to 100° F., became slightly cyanotic, complained of pain in the right lower chest and upper abdomen radiating into the right shoulder and scapular region. A pleural friction rub was heard in the right lower chest between the axillary lines. The electrocardiogram on the seventh day in the hospital (Fig. 1*B*) showed a slight depression

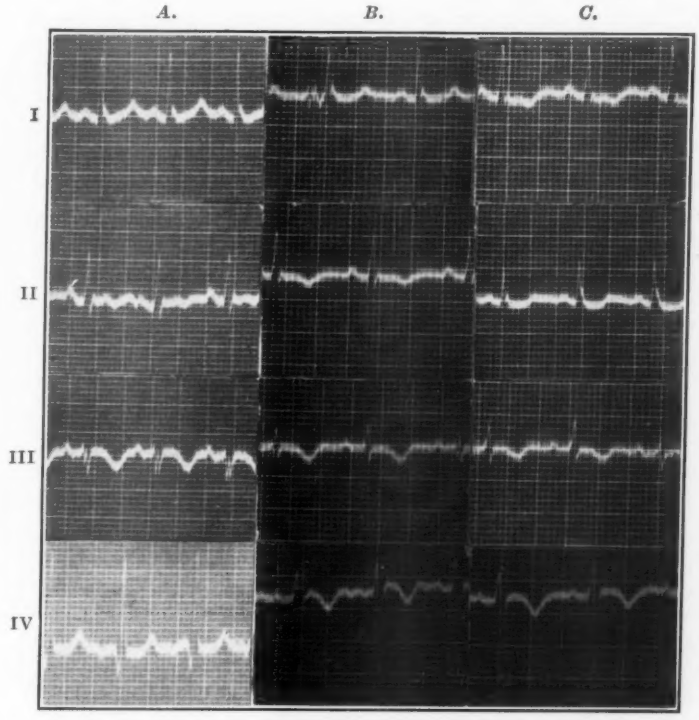

Fig. 1.—Successive electrocardiograms. *A*, when first seen; *B*, on the seventh hospital day; *C*, on the eleventh hospital day.

of S-T_1 and notably different from the first tracing, absent Q_4, a Deep S_4, and inverted T_4. (The patient had received digitalis 0.1 gm. (gr. 1½) three times daily for six days. His weight was 180 pounds.) The electrocardiogram on the eleventh day in the hospital (Fig. 1*C*) showed no change except inverted T_1 and depressed ST_2. A loud systolic murmur was heard localized in the pulmonic area. There was a loud superficial sounding, scratchy to-and-fro murmur, similar to a pericardial friction, heard in the third and fourth interspaces inside the midclavicular line. Signs of another infarct were found on the left. The patient grew progressively worse and died on the nineteenth day in the hospital.

A diagnosis of multiple pulmonary emboli was made, which emboli were thought to derive from a mural thrombus in the right heart, the result of a coronary oc-

clusion. No other origin for a pulmonary embolus could be found; no immediate or remote symptoms or sign gave the slightest clue.

Post-Mortem Examination (J. B. H.).—The body was that of a well-developed and well-nourished white male. Examination was made three hours post mortem. On opening the *pleural* cavities, each was found to contain amber fluid and shreds of fibrin. Partly organized fibrinous adhesions were present between the right lower lobe and the diaphragm and thick layers of fibrin covered the left lower lobe and a portion of the left upper lobe. About 500 c.c. of fluid was present in the right pleural cavity and 1,000 c.c. in the left. Both *lungs* were markedly increased in weight, the right weighing 820 gm., the left 600 gm. Firm, airless, brown and purplish brown areas (1.5 to 4 cm. in diameter) were present in the lower portion of the left upper lobe, the left lower lobe and the right lower lobe. Intervening tissue was crepitant and yellowish gray, except in the left lower lobe where it was atelectatic. Both branches of the *pulmonary artery* were occluded by dull-surfaced, firm, brownish and purplish red blood clot. That filling the right branch was more extensively and firmly adherent to the vessel wall than the clot in the left. Ramifications extended into smaller pulmonary vessels but were blunt and short in the upper lobes, whereas in the lower portions of the lungs they could be traced to the firm brownish purple areas at the periphery. These distal clots were only weakly attached to the vessel walls and could be extruded by slight pressure. The main pulmonary artery contained only fluid blood. Microscopical examination of the large branches of this vessel showed partial organization of the contained clot. This was more extensive in the right. The vessel walls were well preserved and, except for a few lymphocytes in the adventitia, were negative. The firm, rubbery areas in the lungs showed an infarct type of necrosis, with extensive hemorrhage and an infiltration of polymorphonuclear neutrophiles at the periphery. A large artery containing a blood clot showing slight early organization was present in an occasional section. Capillaries in alveolar walls were distended with blood. Some alveoli were dilated and many contained macrophages with included hemosiderin. Occasionally fibrin and partly organized fibrin were found. The alveoli in the left lower lobe were partially collapsed. The *heart* weighed 320 gm. and was of average size. The muscle was firm, brownish red and both grossly and microscopically negative. The myocardium of the right ventricle was markedly thickened (0.5 to 0.9 cm.) but that of the left ventricle was only slightly hypertrophied (1.5 cm.). The endocardium and all valves were negative. The coronary arteries presented a few patches of yellow intimal thickening but were widely patent. The *spleen* presented a slight hemosiderosis. The *liver* was increased in weight to 1,920 gm. and showed accentuated red, central markings. *Gastrointestinal tract, pancreas, kidneys,* and *adrenals* were negative. The *left common iliac vein* contained a propagated thrombus 5 by 2 by 1.5 cm., unattached to the vessel wall. This was in continuity with a clot filling the *hypogastric vein.* Veins of the *prostatic* and *vesicle plexus,* on the left, were filled with brown blood clot. This could be pressed from some vessels but in most was firmly adherent to the wall. Microscopic examination revealed varying degrees of organization, and one vessel contained organized, calcified thrombus. Vein walls were negative. Vessels on the right, corresponding to the above, contained fluid blood and a small amount of soft postmortem clot. The left *seminal vesicle* presented a thick wall and contained clear, viscid fluid. The lumen was dilated and the lining surface smooth. Microscopically the wall was formed of dense hyaline connective tissue and contained patches of calcification. The epithelium was flat, and normal mucosal foldings were absent. Pink-staining masses of coagulated albumin filled the lumen. The other seminal vesicle was negative. *Prostate, testes, and bladder* were negative.

Diagnosis.—Embolic and secondary thrombotic occlusion of the main branches of the pulmonary artery; thrombosis of the veins of the left prostatic and vesicle plexus with propagated thrombus in the hypogastric and common iliac veins; old vesiculitis

(left); infarcts of lungs; myocardial hypertrophy (right ventricle); fibrinous pleuritis; hydrothorax; atelectasis (left lower lobe); hemosiderosis of spleen; acute passive congestion of the liver.

COMMENT

Pulmonary embolism is readily recognized postoperatively or following phlebitis by sudden onset, dyspnea, with or without pain, cough or hemoptysis, usually with circulatory collapse. The diagnosis may be considered in any female who has borne children or has had pelvic inflammation, because of the possibility of recent or old pelvic phlebitis. But in a previously healthy young man complaining of gradually progressive dyspnea and cough of three weeks' duration and with no history suggesting genitourinary or other disease likely to cause phlebitis, we submit that an unusual myocardial disease of coronary origin, primary pulmonary sclerosis, or even pulmonary neoplasm is more likely. That this reasoning was totally wrong in this case has led us to make this report.

One feature of the first electrocardiogram, namely, upright T_4 with persistence of the Q-wave, led one of us (R. S. P.) to suspect pulmonary embolism, only to rule it out on the above mentioned erroneous reasoning. This change not characteristic of coronary disease was present in two cases of pulmonary embolism reported by McGinn and White.[1] Of the other electrocardiographic signs mentioned by them, namely, prominent S_1, and low origin of T_1, gradual "staircase ascent" of S-T_2, and especially stressed by them, Q_3 and late inversion of T_3, only the late inversion of T_3 was present. Subsequent electrocardiograms in the present case showed alterations in the T-waves possibly due to digitalis. The absence of Q_4 with a deep S_4 and inversion of T_4 may have been due to faulty application of the electrodes by the nurse or technician while the patient was in the hospital, a common cause of unusual features in Lead IV. In the first tracing the electrodes were accurately placed by one of us (R. S. P.).

SUMMARY

An unusual case of pulmonary embolism from unrecognized and asymptomatic pelvic phlebitis in a previously healthy male of thirty-three years is reported.

Accurate electrocardiographic examination with especial reference to Lead IV may be of great importance.

REFERENCE

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Department of Reviews and Abstracts

Selected Abstracts

Gupta, J. C.: The Reflex Adjustment of the Circulation and the State of Respiration after Decerebration. Ztschr. f. Kreislaufforsch. 28: 492, 1936.

The heart is slower and the mean blood pressure is lower in decerebrate cats and dogs than in narcotized ones. This difference is due to a greater tonic reflex action of the pressor receptor nerves in the former as shown by a lack of difference after resecting these afferent nerves.

L. N. K.

Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D.: Calculation in Cardiac Output From Blood Pressure Measurements Before and After Meals. Am. J. Physiol. 116: 551, 1936.

Cardiac outputs can be calculated from the changes in blood pressure and pulse wave velocity following a meal with an accuracy of the same order as that obtained under basal conditions.

Changes in cardiac output after a meal cannot be represented by a simple plateau curve.

The changes in blood pressure and pulse rate are similar to those described by others. The calculated effective peripheral resistance is lowered. Diastolic pressure changes are not a measure of those in effective peripheral resistance. Peripheral dilatation is always associated with a decrease in distensibility of the larger central vessels, as indicated by pulse wave velocities. A constriction of the large vessels is suggested as a possible cause, and presumably these vessels act as an adjustable reservoir.

A method of recording sternal movements is described and is utilized for the timing of the start of cardiac ejection. The relationship of such curves to electrocardiograms is discussed.

The time relations of the electrical and mechanical changes so measured before and after meals are described.

A source of error in the preservation of acetylene samples over mercury is mentioned.

AUTHOR.

Collens, William S., and Wilensky, Nathan D.: New Skin Thermometer for Diagnosis of Peripheral Vascular Disease. Am. J. Surg. 33: 157, 1936.

The instrument consists of a mercury therometer, similar to the ordinary clinical thermometer but with a finer bore to permit a rapid rise of the mercury column. Skin temperature readings, during rising skin temperature, were taken by means of this with the thermocouple as control. The greatest deviation was 1.0° F. The time required for contact of the thermometer with the skin was not given.

H. M.

Battro, A., and Lanari, A.: Intra-Arterial Inection of Acetylcholin. Rev. argent. de cardiol. **3:** 31, 1936.

Intra-arterial injection of acetylcholin (0.04 gram) is an excellent, simple and harmless test to investigate in diseases of the peripheral arterial system in order to determine (a) organic from functional disturbances, (b) the site of the occlusion in cases of organic lesions, and (c) the conditions for collateral circulation. This information is gained through the study of pain, rubescence, and oscillographic variations caused by the drug.

In functional disturbances the changes produced do not differ from those observed in normal individuals. In organic lesions, when the main artery is occluded, the oscillographic index remains unchanged below the site of occlusion, and the conditions for collateral circulation are gauged by the rapidity of appearance, degree, and distribution of the rubescence.

AUTHOR.

Cushing, E. H.: Chronic Constrictive Pericarditis, Electrocardiographic and Clinical Studies. Am. J. M. Sc. **192:** 327, 1936.

Eleven patients with adhesive mediastinopericarditis, upon whom pericardectomy was performed, all had electrocardiograms with QRS complexes of low amplitude. The T-waves were low in voltage. Following pericardectomy the QRS voltage increased in four of seven cases.

AUTHOR.

Levine, Harold D., and Levine, Samuel A.: An Electrocardiographic Study of Lead IV With Special Reference to the Findings in Angina Pectoris. Am. J. M. Sc. **191:** 98, 1936.

Electrocardiographic study was made of forty-four patients who were subsequently examined post mortem. The customary three leads were taken and, in addition, fourth leads with the anterior electrode at the fourth left sternal border and at the apex and with the indifferent electrode on the left leg.

In twelve instances in which the Q-wave was absent in Lead IV, either at the left sternal border or at the apex, infarction of the ventricle was found. Two cases with bundle-branch block and one of tuberculous pericarditis with absent Q_4 showed no infarction.

There were fifteen patients with small Q_4 (2 mm. or less), about half of whom had infarction and the other half did not.

Upright T-waves in Lead IV were found when no infarction was present, and, in fact, where there was no significant heart disease.

In eleven cases in which the heart was normal and in one with posterior infarction, Lead IV was normal.

Evidence is presented to show that myocardial infarction is not uncommon in angina pectoris when there is no clinical evidence of a previous coronary thrombosis. Sixteen of 100 cases showed an absent Q_4 and in eleven of these the customary three leads were essentially normal.

Apart from the changes in Lead IV which occur during the acute phases of coronary thrombosis, we believe that the absence of Q_4 is very helpful in the diagnosis of a previous myocardial infarction, except when bundle-branch block is present.

Lead IV is indispensable in the proper diagnosis of certain cases of heart muscle disease.

AUTHOR.

Levine, Harold D.: The Effect of Various Altered Cardiac Mechanisms on Lead IV. M. Papers, Christian Birthday Volume, p. 87, 1936.

Abnormalities generally indicating myocardial infarction may occur in Lead IV in bundle-branch block without infarction.

Auricular fibrillation and flutter per se produce no changes in the QRS-waves of Lead IV.

T-waves are so frequently upright in rheumatic and thyrotoxic heart disease with or without auricular fibrillation that the inference whether or not infarction of the heart is present cannot be drawn from these changes.

The absence of the Q-wave is just as valuable in the diagnosis of myocardial infarction in the presence of auricular fibrillation as with normal sinus rhythm.

In exceptional instances the absence of a Q-wave in Lead IV may be associated with posterior infarction.

AUTHOR.

Graybiel, Ashton, and White, Paul D.: Complete Auriculo-Ventricular Dissociation. A Clinical Study of Seventy-Two Cases With a Note on a Curious Form of Auricular Arrhythmia Frequently Observed. Am. J. M. Sc. 192: 334, 1936.

Seventy-two cases of complete A-V dissociation are briefly analyzed. Coronary heart disease was associated in 47 of the patients, congenital heart disease in 4, possible congenital heart disease in 2, rheumatic heart disease in 3, cardiovascular syphilis in 3, and possible chronic diphtheritic heart disease in 4, while the remaining 9 cases were of mixed or entirely uncertain etiology. Two-thirds of the cases (48) were male and one-third (24) were female; it was particularly in the coronary disease and syphilitic groups that the males predominated (36 to 11 in the former and 3 to 0 in the latter).

The heart disease responsible for the block in these cases affects the clinical course, treatment and prognosis far more than does the block itself.

Attacks of dizziness, syncope, or convulsions, symptoms related to the block itself, were present in 44 of the 72 cases; in 4 instances they were the probable cause of death. Adrenalin and ephedrine were the only drugs found valuable in the treatment of these attacks.

The prognosis of those patients in this series with coronary heart disease was generally very poor, although there were striking exceptions; for those with congenital or old diphtheritic heart disease it was good, while for those with luetic or rheumatic disease it was fair.

A form of auricular arrhythmia frequently observed in these cases is discussed.

AUTHOR.

Campbell, Maurice, and Gordon, F. W.: The Quinidine Treatment of Auricular Fibrillation. Quart. J. Med. 5: 205, 1936.

The after-results of treatment with quinidine have been followed in two series of patients, one first treated in 1923-28, and the other in 1929-34; almost all have been followed up to December, 1934, or until fibrillation recurred. Quinidine restored normal rhythm in 64 per cent of 135 cases. In 34 per cent it is still maintained after an average period of nearly four years. In 30 per cent it was restored, but fibrillation recurred after an average period of two years. In 36 per cent quinidine failed to restore normal rhythm, or did so for such a short time that it was of no practical importance.

Of the earlier series 25 per cent after nine years, and of the later series 39 per cent after two years still maintain normal rhythm. Quinidine is, therefore,

an effective and often a lasting treatment for auricular fibrillation; its success depends on the careful selection of suitable patients. The duration of fibrillation before treatment, the size of the heart, and the etiology are all important in estimating the chance of restoring normal rhythm and, even more so, of maintaining it for a long period.

Nearly half the cases in which fibrillation had been present for less than a month still maintain normal rhythm, about a quarter of those in which it had been present between one and six months, but few of those in which it had been present for longer. When the heart was only slightly enlarged, 38 per cent, when it was moderately enlarged, 18 per cent are satisfactory, but when it was greatly enlarged only 5 per cent are still satisfactory. Standards for the size of the heart for different body weights have been suggested to help in deciding if quinidine should be used.

The etiology is important and is the main factor in deciding if continuous after-treatment is necessary. In cases in which there is mitral stenosis, the period of restored normal rhythm is not likely to exceed four years. Only 14 per cent of our cases with valvular disease maintain normal rhythm, and in most of these the heart is slightly, if at all, enlarged. Two very successful results were in patients with a history of rheumatic fever but no evidence of mitral stenosis; they have maintained normal rhythm for over eight years without continuing to take quinidine. But in the others with mitral stenosis the average period is as yet only twenty-seven months, and most of them have continued to take it. With appreciable enlargement of the heart, therefore, continuous after-treatment with quinidine is necessary. In those who have relapsed, the average period of restored normal rhythm was nearly two years.

In cases in which fibrillation is present without mitral stenosis or goiter, the selection of cases may be made more leniently, and under favorable circumstances the rhythm may remain normal for ten years or longer. In 39 per cent it is still maintained after an average of five years. In the fifteen who could be classified as having no signs of heart disease except the arrhythmia, it is still maintained in 70 per cent after the same period. After-treatment is not generally needed for more than three months, but, if relapse occurs on omitting quinidine, a second course should be given, and, if successful, quinidine should be continued for longer. In those who have relapsed, the average period of restored rhythm was over two years.

When fibrillation is due to a goiter, nearly all cases should be treated, as, when necessary, an operation will change an unsuitable case into one suitable for quinidine. The duration of fibrillation and even the size of the heart are much less important in this group. A lasting success should generally be achieved, and normal rhythm is still maintained in 80 per cent after an average of forty months. In three patients it has been maintained for nine years and in three others, for four years. With partial thyroidectomy continuous after-treatment with quinidine is not called for. If the patient is treated without operation, the continuous administration of quinidine may be, but is not always, needed.

Thorough digitalization is important before starting treatment by quinidine. Any infection, even a trivial one, may prevent success. Except for the possibility of embolism, which is not a grave risk, serious complications are rare.

Quinidine has an important place in the treatment of auricular fibrillation—provided the cases are carefully selected. The ordinary patient seen in hospital is quite unsuitable; the risk is too great; and, if fibrillation is arrested, it generally returns too soon. Satisfactory results are obtained by paying attention to three main criteria: the absence of congestive failure, of a greatly enlarged heart, or of a long history of fibrillation.

The case is eminently suitable for treatment with quinidine and should certainly be given this opportunity of regaining normal rhythm if there have been no signs of failure, and if the heart is only slightly enlarged (less than 13 cm. maximum transverse diameter in a patient of about 10 stones), and if fibrillation has been established less than one month.

The case is not suitable if there has been gross congestive failure or if any signs of failure persist after treatment with rest and digitalis, or if the heart is greatly enlarged (more than 14 cm. maximum transverse diameter in a patient of about 10 stones), or if fibrillation has been established for six months. The presence of any one of these three usually means that treatment with digitalis should be preferred. In intermediate cases the decision will be made according to how nearly they fall into one or other of these groups.

In cases with mitral stenosis these conditions must be strictly observed. Less attention need be paid to them if fibrillation is due to a goiter, as, if necessary, partial thyroidectomy will convert an unfavorable case into one favorable for quinidine.

AUTHOR.

Gelman, I., and Pusik, W.: The Pathological and Electrocardiographic Characteristics of the Heart in Senility. Ztschr. f. Kreislaufforsch. **28**: 570, 1936.

Two case reports from Moscow are presented of individuals 112 and 122 years of age! The first had hypertension, cardiac hypertrophy, a four-plus Kahn test, senile dementia, emphysema, and a normal electrocardiogram. He worked on the land until the age of 103 without serious illness and then became an invalid. The second patient worked on the soil until the age of 118. He had had an amputation of the penis for carcinoma at the age of 100 without ill effects and had a long-lasting pyelonephritis at autopsy. An hypertrophied left ventricle was found. and slight coronary sclerosis and emphysema.

L. N. K.

Milew, A.: An Atypical Case of Myocardial Infarct. Ztschr. f. Kreislaufforsch. **28**: 609, 1936.

A case of myocardial infarct with paroxysmal tachycardia and bundle-branch block is presented. The patient had no pain.

L. N. K.

Sike, H.: Eosinophilic Myocarditis as an Idiosyncratic-Allergic Disease. Frankfurt. Ztschr. f. Path. **94**: 283, 1936.

After a fair review of the heterogeneity of the pathological picture of myocarditis of uncertain origin (the group which in this country has usually been spoken of as "idiopathic myocarditis"), the author points out that an eosinophilic infiltration has been described a number of times in cases other than those due to diphtheria or trichiniasis. He then describes two patients, both of whom had syphilis, who were treated with moderate amounts of antisyphilitic arsenicals, developed severe arsenic dermatitis, and died within a few weeks in the presence of rather abrupt heart failure, dyspnea, pulmonary congestion, cyanosis, low temperature, and faint heart sounds. Neither had cardiovascular syphilis. At autopsy there was found myocarditis characterized chiefly by infiltration of eosinophilic leucocytes, the presence of multinucleated giant cells, broken muscle fibers, and focal necroses. (It should be recalled that eosinophilia is not uncommon in arsenic dermatitis.) After lengthy discussion he suggests that the myocarditis found in these two cases (and in three others in the literature) is the result of an allergic reaction or of an idiosyncrasy of the patients to arsenic.

J. M. S.

Moser, A.: Congenital Absence of the Tricuspid Orifice. Ztschr. f. Kreislaufforsch. **28:** 521, 1936.

Three cases are reported in which the absence of the tricuspid orifice was associated with a fusion of the two auricles and a defect of the ventricular septum (Wieland's disease). In addition, there was a hypertrophied left and an atrophied right ventricle. The literature is reviewed.

L. N. K.

Gross, Louis, and Fried, B. M.: Lesions in the Auriculo-Ventricular Conduction System Occurring in Rheumatic Fever. Am. J. Path. **12:** 31, 1936.

One hundred ten human hearts have been examined in order to determine the nature and frequency of the lesions occurring in the Tawara node and bundle of His in rheumatic fever. Sixty of these cases represent active rheumatic fever; 25 cases, inactive rheumatic fever; and 25 cases, nonrheumatic conditions. It has been shown that in active rheumatic fever there occurs a variety of inflammatory and vascular phenomena within the horizontal conduction system as well as in the surrounding tissue. Even when studied in few representative specimens from each bundle, the incidence of these lesions was approximately 66 per cent in the active material. It is probable that a study of more sections would have indicated a higher incidence. Very few of these lesions are of a specific or highly characteristic nature. The inactive rheumatic cases showed few pathological changes. This is in keeping with the functional differences observed as between these two groups. Attention has been called to the high incidence of inflammatory lesions in the collagenous extension of the septum fibrosum and a discussion of the possible mechanisms concerned with the spread of the rheumatic infection to the bundle tissue is given. A description of the topographical relations of the horizontal conduction system in the human heart, together with the findings in twenty-five nonrheumatic control cases, is also given.

AUTHOR.

Friedberg, Charles K., and Gross, Louis: Pericardial Lesions in Rheumatic Fever. Am. J. Path. **12:** 183, 1936.

Gross and microscopic pericardial lesions are described in sixty-eight cases of active and nineteen cases of inactive rheumatic heart disease. These cases were divided into five clinical groups depending on the course of the disease. The lesions as a whole fell into three characteristic histological patterns which could be correlated with the clinical course. The earliest lesions (first pattern) found in patients who succumbed to a first attack of rheumatic fever consisted primarily of swelling and degeneration of the collagen in the lamina propria, inflammation and vascularization of that layer and subjacent adipose layer, proliferation, desquamation, and pseudogland formation of the epithelial layer, exudation of fibrin, and Aschoff body formation. In the cases with recurrent attacks (second pattern) there were marked thickening of the membranes, universal adhesions and a tendency to obliteration of the pericardial cavity, organization of the inflammatory exudate, and formation of layers. In the chronic slowly progressive and healed cases (third pattern), there were mild lesions characterized by the infiltration of round cells into the deeper portions of the lamina propria and adjacent areas and by increased vascularization and structural alterations of blood vessels. Statistical data from this study indicate the almost invariable presence of pericardial inflammation in rheumatic heart disease. A description is also given of the age period changes in the histology of the normal pericardium.

AUTHOR.

Gross, Louis, and Friedberg, Charles K.: Lesions of the Cardiac Valve Rings in Rheumatic Fever. Am. J. Path. 12: 469, 1936.

The authors studied the valve rings of 40 nonrheumatic control hearts and 97 rheumatic hearts. The latter were segregated into six clinical groups according to the presence or absence of Aschoff bodies and the occurrence of one or more attacks of acute rheumatic fever. The valve ring is defined in detail but roughly refers to the most proximal portion of the valve cusp excluding auricular myocardium. The normal rings rarely showed capillaries and never inflammatory cells. The rheumatic rings grossly showed a widening and irregularity in place of the usual fine sharp line of attachment. Microscopically, there were extensive inflammatory lesions which usually involved all of the valve rings. These consisted of extensive infiltration of inflammatory cells, vascularization, edema, scarring, and, except in the last group, Aschoff bodies. These lesions usually involved all four rings, but the pulmonic ring was the most likely to be free. Fibroelastic reduplications were frequently present in the subaortic and subpulmonic angles, and there was frequently inflammation of the intervalvular fibrosa. The valve rings are stressed as strategic sites because it is believed that inflammation of the valves and neighboring sites occurs by spread from the rings.

AUTHOR.

Von Raab, W.: The Central Forms of Arterial Hypertension. Ergebn. d. inn. Med. u. Kinderh. 46: 452, 1934.

Separation of the blood vessels from the central nervous system shows that blood vessels have two types of tonus; therefore the vasomotor centers are not alone responsible for high blood pressure. Hypertension occurring during hemorrhage in the brain or resulting from brain tumors may be partly due to some stimulation, partly to direct mechanical pressure on the vascular supply of the vasoconstrictor centers, and partly due to pressure itself on centers, or perhaps it may be caused by destruction of the depressor centers. In poliomyelitis with acute hypertension localized lesions in the medulla have been found. Similar changes seem to be present in cases of encephalitis associated with hypertension. The presence of local circulatory disturbances in vasomotor centers of the brain and medulla in essential hypertension are indicated by the following: (1) frequency of arteriosclerotic changes; (2) occurrence of severe chronic hypertension in patients with marked cerebral arteriosclerosis whose kidneys are not apparently diseased; (3) abnormalities in the arteries in the medulla and pons in cases of essential hypertension; (4) increasing lack of elasticity of the arteries in the brain; (5) increasing sclerotic changes in the smallest brain vessels and narrowing of the cerebral vessels in older people.

The frequent occurrence of hypertension in endocrine disturbances, as suprarenal cortical hypertrophy, pituitary basophilism, and diabetes mellitus, as well as the hypertension associated with polycythemia, may be based principally upon arteriosclerosis in the vasomotor centers and perhaps on direct hormonal stimulation of these centers. Several factors indicate the importance of the central nervous system in the pathogenesis of essential hypertension, such as (1) hypersensitivity of the vasomotor centers to changes in the concentration of carbon dioxide in the blood and increasing response to carbon dioxide of the vasomotor centers in older people; (2) increased sensitivity of the vasomotor centers to decreased oxygen in the inspired air in older persons and persons with hypertension; (3) abnormally marked increase in blood pressure in persons with hypertension and old persons resulting from psychic irritation, muscular exercise, and pain; (4) decrease of an abnormally

high blood pressure during sleep and anesthesia; (5) metabolic abnormalities in essential hypertension, such as elevated metabolism and hyperglycemia, which are probably produced centrally; (6) increased oxygen utilization by the brain in essential hypertension, probably due to a decreased cerebral blood flow; (7) decrease of the blood pressure in hypertension during diathermy of the brain stem; (8) lowering of the blood pressure after lumbar puncture; and (9) depressing effect of adrenalin in hypertension. Essential hypertension appears to be caused mainly by overstimulation and hypersensitivity of the vasomotor centers.

Factors which play rôles in the development of arteriosclerosis in hypertension are heredity and constitution, hormonal influences, infections, and abuses of nicotine and alcohol. The chief factor responsible for organic changes in the vessels of the brain is the content of cholesterol and vitamin D in the diet. These substances are present in butter and milk, animal fat, and the yoke of egg. Some observations on people not living in Europe whose diet is poor in cholesterol and vitamin D show that they have arteriosclerosis and hypertension very rarely. Further statistical investigation is desirable. Some therapeutic procedures, such as administration of sedatives, lumbar puncture, application of diathermy to the brain stem, administration of drugs which increase the circulation in the brain, and perhaps diet, work against the mechanism producing hypertension of central origin; however permanent effects cannot be expected. It is specially important in hypertension of central origin to avoid psychic irritation.

G. R.

Wezler, K., and Böger, A.: The Boundaries of the Arterial Pressure Dome in Man. Ztschr. f. Kreislaufforsch. **28**: 391, 1936.

The pressure dome converts the intermittent flow from the heart into a constant flow in the capillaries, and it determines the form of pulse in the arteries. The physical methods of measuring volume flow are based on this concept. It is shown that the effective length of the pressure dome can be measured by dividing by 4 the product of the pulse wave velocity in the aorta-iliac tube and the duration between the peak of the primary and dicrotic waves in the femoral pulse (which is the pulse wave length).

In determining the pulse wave velocity (a) the length of the tube is measured from the root of the aorta to the point where the femoral pulse is recorded and (b) the time lag of the pulse in the femoral behind the subclavian is multiplied by 1.28.

The length of the pressure dome depends on the body size and is related to the stroke volume. It is longer in tall persons. Its lower limit varies from the iliac to the femoral artery. In hypertension it extends to the muscular arteries. The length of the pressure dome also increases with age. These deductions are based on an analysis of optically recorded subclavian and femoral arterial pulses.

L. N. K.

Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative Prediction of Effects on Blood Pressure of Neurosurgical Treatment of Hypertension. Proc. Staff Meet. Mayo Clin. **11**: 401, 1936.

It is important to know before operation what the effect of the neurosurgical treatment of hypertension will be on the blood pressure. Certain clinical observations are important, but frequently they do not allow accurate prediction. There is stimulation, therefore, to search for a more accurate method of predicting the effect of operation on the blood pressure. Anesthesia induced by the intravenous injection of a solution of pentothal sodium in sufficient amounts to cause a maximal

increase in the temperature of the skin of the toes is a safe procedure if the drug is administered expertly. The blood pressure resulting from this procedure constitutes an accurate reflection of that resulting from bilateral resection of the splanchnic nerves and the first and second lumbar ganglions and partial resection of the celiac ganglions and suprarenal glands. Preoperative prediction of the immediate effect of operation on the blood pressure can therefore be made safely and accurately.

AUTHOR.

Edwards, Edward Allen: The Orientation of Venous Valves in Relation to Body Surfaces. Anat. Rec. **64**: 369, 1936.

A seemingly constant orientation of the valves of human veins of the extremities is described. The vein at the site of the valve is elliptical in cross-section, the major axis of the ellipse being parallel to the skin or its tangent. Within the vein at the valve site, the two cusps rise from the long curves of the ellipse so that the aperture between their free margins is also parallel to the overlying skin. The advantage of this arrangement is that the compression transmitted to the veins by overlying structures produces secure apposition of the cusps to each other and thereby insures the competency of the valve.

E. A.

Ochsner, H. C., and Conner, H. M.: Lipemia Accompanied by Atheromatous and Occlusive Vascular Disease: Report of a Case and Partial Review of the Literature. Ann. Int. Med. **10**: 258, 1936.

Among the disorders of lipid metabolism is the so-called essential xanthomatosis with involvement of the skin, mucous membranes, and tendon sheaths, or viscera. The vascular system also may be involved in these xanthomatous changes. A case is reported in which the changes in the vascular system were associated with a lipemia. The patient eventually died from the effect of coronary thrombosis. There was nothing to suggest Gaucher's disease, and Schüller-Christian's, Niemann-Pick's and Tay-Sachs' diseases were readily excluded on the basis of the patient's age. The case was classified as one of essential xanthomatosis with localization primarily in the vascular system.

E. A. H.

Armentano, L., Bentsáth, A., Béres, T., Rusznyak, St., and Szent-gyorgyi, A.: Concerning the Influence of Substances of the Flavoral Group Upon the Permeability of the Capillaries—Vitamin P. Deutsche med. Wchnschr. **62**: 1326, 1936.

The authors expand the preliminary note in *Nature* of July 4, 1936, concerning the actions of these substances and append cases for illustration. It was previously noted that whole lemon juice or paprika would relieve certain cases of purpura which were unaltered by pure ascorbic acid. Several extracts were then made from lemon juice, the various methods of extracting being given in some detail and one preparation was obtained in crystalline form to which is given the name "citrin." These substances were used in treating cases of "vascular purpura;" that is, cutaneous purpuric spots affecting young adults apparently well in other respects. Platelets numbered from 180,000 to 280,000, capillary resistance was low (10 mm. Hg.), capillary filtration was rapid and protein was present in the capillary filtrate. The use of "citrin" brought about disappearance of purpuric spots within ten days, and return of the capillary resistance and other factors to normal. Unfortunately

there is no notation of the number of platelets after treatment. The authors mention four similar cases in which the platelet counts were not decreased and in which the drug was of no use. Last, ten instances of hemorrhagic diathesis occurring during the course of a variety of diseases as chronic infections, nephritis, and diabetes are reported in which immediate, if only temporary, relief was afforded in all instances, even when steady progress of the original disease led to death. Although the data in these last ten cases is insufficient, the results arrest one's attention with regard to possibilities of the drug.

J. M. S.

Prinzmetal, Myron: Studies of the Mechanism of Circulatory Insufficiency in Raynaud's Disease in Association With Sclerodactylia. Arch. Int. Med. 58: 309, 1936.

In sclerodactylia the areas of greatest circulatory insufficiency correspond with the areas of greatest shrinkage of skin and subcutaneous tissue. Skin temperature of the digits follows room temperature much more closely than it does in Raynaud's disease without sclerodactylia. Various vasodilatation procedures, including sympathectomy, failed to disturb equality of skin and room temperature. Artificial sclerodactylia was produced in normal fingers by constricting them with pressures between 60 and 90 mm. Hg. Skin temperature, taken through a small opening in the constricting device, closely followed room temperature, and vasodilatation procedures failed to disturb this equality.

It is concluded that arterial occlusive phenomena in sclerodactylia are probably caused by the tight skin and subcutaneous tissue, and that attempts to dilate the vessels in the affected area by heat or sympathectomy do not, and should not be expected to, relieve sclerodactylia. In one patient incision of skin was tried; no retraction of skin edges and no improvement followed. The most rational therapeutic procedure is the use of alternate suction and pressure. This was found to be helpful in some cases.

AUTHOR.

Galloway, R. J. M.: The Changes in the Appearance of the Wall of a Muscular Artery Between Diastolic and Systolic Blood Pressures. Am. J. Path. 12: 333, 1936.

The number of folds present in the intima and internal elastic lamiae of muscular arteries is a criterion for the degree of contraction present in the muscle tissue of the media.

The degree of post-mortem contraction in excised arteries is not uniform. It varies not only in different arteries from the same individual but in different parts of the same segment of an artery. These differences are due largely to differences in stimuli produced in excising the arteries, although other factors also probably play some part.

Relaxed excised arteries, distended by pressures equivalent to at least 80 mm. Hg or more, show a loss of waviness of the intima and of the elastic tissues in the wall. The elastic fibers in the media and in the external elastic lamina lose their wavy contour before the fibers in the internal elastic lamina.

The changes in the artery wall during the passing of the pulse wave probably vary between a moderate folding of the intima and internal elastic lamina at diastolic blood pressure, and a lesser degree of this folding at systolic pressure, a change that may even extend to a complete loss of folds in these layers.

AUTHOR.

Gottesman, J.: Arteriovenous Aneurysm of Hand. Am. J. Surg. 33: 323, 1936.

A single case report is given. There was a distinct pulsation over the thumb, thenar eminence, the proximal half of the index finger, and the adjacent palm. Pain at times was severe; bleeding was frequent following trauma. Because of bleeding and infection the thumb and forefinger were amputated. Pathological examination showed the distal phalanx of the thumb and the middle phalanx of the index finger to be permeated by large, thick, anastamosing vascular channels. In most cases it was impossible to identify the vessels as arteries or veins.

H. M.

Theis, Frank V., and Freeland, M. R.: Peripheral Circulatory Diseases. Effect of Alternating Positive and Negative Pressure Treatment on Venous Blood and the Skin Temperatures: Preliminary Report. J. A. M. A. 107: 1097, 1936.

Studies were made of the effect of alternate suction and pressure, of heat, and of a combination of the two, on several factors in vascular insufficiency in the lower extremities. Emphasis is laid on skin temperature readings on the toes and on values for O_2 and CO_2 in the blood from the upper part of the saphenous vein of the affected limb. When heat was used, some degree of sweating was usually effected. When suction and pressure was used, it was used for one hour, measurements being taken before and after the procedure.

Reasoning from values obtained for the three variables, skin temperature, O_2 saturation, and CO_2, the authors conclude that the effect of suction and pressure alone is to increase tissue metabolism rather than to increase blood flow. They base this conclusion mainly on a slightly reduced average O_2/CO_2 ratio in venous blood under suction alone and on an increased average O_2/CO_2 ratio in venous blood resulting from reflex vasodilatation caused by heat. They agree with previous authors that heat should be used with suction and pressure but believe that suction and pressure is effective by its increasing tissue metabolism rather than by its increasing blood flow.

H. M.

Horton, Bayard T., Brown, George E., and Roth, Grace M.: Hypersensitiveness to Cold With Local and Systemic Manifestations of a Histamine-Like Character. J. A. M. A. 107: 1263, 1936.

Certain subjects exhibit abnormal local and systemic reaction to cold. The local effects on that part of the skin exposed to cold include redness, swelling, and increased skin temperature on removal. There is flushing of the face, a sharp fall in blood pressure, a rise in pulse rate, a tendency to, or the actual development of, syncope. When a tourniquet is placed on an arm and that hand is placed in cold water, there is no systemic reaction, but one or two minutes after removal of the tourniquet the systemic reactions are more severe than when no tourniquet is used. In six cold-sensitive subjects the same clinical syndrome was produced by administration of histamine. Analyses of gastric free hydrochloric acid before and after eliciting the response to cold showed differences similar to those found by injection of histamine. Attempts to isolate histamine from the blood at the height of a systemic reaction to cold have been unsuccessful and were also unsuccessful when histamine was injected in quantities sufficient to produce shock.

Some of the patients have been susceptible to exposure to cold for many years. Systemic desensitization to cold is accomplished successfully in most patients by frequent short exposure of the hands to cold water. The authors refer to a case in the literature in which a patient was desensitized to cold by administration of histamine. (Bray.)

H. M.

Lederer, Emil: Studies of the Capillary Circulation. Part I. Basic Principles—the Method. Part II. The Action of Different Drugs Upon the Circulation. Arch. f. exper. Path. u. Pharmakol. **182**: 182 and 363, 1936.

Part I. Studies of the nail beds of twelve children by means of a capillary microscope were made, each on ten or eleven different days. A length of capillary loop 0.4 mm. long was measured out with a micrometer, and the passage of a red blood cell through the capillary was timed by holding down a button connected to a chronometer during its passage. For traversing the 0.4 mm. of capillary from 1.6 to 2.4 sec. were required. Variations in the same child from day to day under similar conditions and at similar times were from 0.2 to 0.8 sec.

Part II. The author then proceeded to study the effect of various drugs. Thyroxin, acetylcholin hydrate, and padutin (a muscle extract) were usually followed by a widening of the capillaries, the appearance of new loops, and an increase in rate of flow, frequently to a point where it was too swift to be timed. It is interesting to note that this occurred in fifteen to thirty minutes after subcutaneous injection of thyroxin in nine of the twelve children. (As is well known, the basal metabolic rate of tissue does not change until much later.) Adrenalin, atropin, and pitressin all slowed the capillary stream, often to the point of complete cessation of flow, and caused disappearance of many capillary loops.

J. M. S.

Faber, B., and Kjaergaard, H.: X-ray Kymograms of Normal and Pathological Hearts. Brit. J. Radiol. **9**: 335, 1936.

This paper is one of the many which during the last few years have appeared in the European literature as evidence of the wide acceptance which this method of examination is gaining. It comes from the Provincial Hospital of Aarhus, Denmark, and is the report of 1,700 cases which have been analyzed by the authors. They find x-ray kymography particularly useful in the examination of mitral hearts. They emphasize the importance of hardness of the wall of the aorta in interfering with aortic movements, also in syphilitic aortitis which thus may become difficult to distinguish from arteriosclerotic aortitis by this method. They also emphasize the value of this method in differentiating between aneurysm and mediastinal tumor. They have never found a "Type 2" shadow (that is the type in which the waves at the base of the heart are more powerful than those in the apex area) in young persons with normal hearts. This they, therefore, consider evidence of pathology though it need not necessarily represent definite anatomical change in the ventricle of the heart. They have seen it especially in coronary sclerosis and after coronary thrombosis. The paper closes with the remark that they believe that kymography is the future method of x-ray examination of the heart.

J. J.

Beck, Claude S.: The Heart as a Surgical Organ, With Special Reference to Development of a New Blood Supply by Operation. Ohio State M. J. **32**: 113, 1936.

A brief résumé of surgical procedures useful for the care of heart disease and wounds is presented. The author then proceeds to explain the basis for surgical treatment of coronary sclerosis by implantation of pectile muscle grafts to the wall of the heart. He describes the experimental development of the operation of animals and then on four patients.

He believes the experimental results on animals and those obtained in the four patients indicate that coronary sclerosis may be treated satisfactorily by such an operation.

H. McC.

Griswold, R. A.: Chronic Cardiac Compression Due to Constricting Pericarditis. J. A. M. A. **106**: 1054, 1936.

In a patient with chronic cardiac compression caused by scar (the Pick syndrome) complete relief was obtained by resection of the constricting scar.

The roentgenokymogram is of value both as a positive diagnostic measure and as evidence of the efficacy of pericardiectomy.

There are advantages of decompression of the heart during the postoperative period by drainage into the pleura.

Several points in the technic of the operative procedure are emphasized, especially in the dissection of the scar from the heart.

AUTHOR.

Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity. Ann. Surg. **104**: 339, 1936.

The unsatisfactory end-results from cervicodorsal sympathetic ganglionectomy for vascular spasm (Raynaud's disease) is attributed to degeneration of the postganglionic fibers and consequent sensitivity to adrenalin when this takes place. A modified dorsal sympathectomy for relief of vascular spasm is described in which only preganglionic fibers are sectioned and the postganglionic fibers are left intact. This operation has been carried out in thirty-three upper extremities in twenty-three patients. Eight of the cases had an associated scleroderma with fibrosis of the soft tissues of the fingers and often with destruction of the terminal phalanges. Clinical results have been extremely satisfactory, as there has been no evidence of recurrence of vascular spasm. The longest interval since operation is eleven months. Three of the cases were tested by the intravenous administration of adrenalin in a dilution of 1 to 250,000. The surface temperature fall in the upper extremities was comparable to that obtained in a sympathectomized foot. If regeneration of nerve fibers at a later date does not cause recurrence of vascular spasm, this should be a satisfactory procedure for eliminating vascular spasm in the upper extremities.

E. A. H.

Blum, Lester, and Gross, Louis: Technic of Experimental Coronary Sinus Ligation. J. Thoracic Surg. **5**: 522, 1936.

Coronary sinus occlusion in the dog's heart produces a rapid increase in the extent of the coronary tree and in the intramyocardial collaterals as determined by the injection technic. In the majority of dogs' hearts thus prepared it is difficult or impossible to induce infarction by subsequent acute occlusion (division between ligatures) of the left anterior descending branch approximately 2 cm. below the aortic ostium of the left coronary artery. A description is given of the technic which we have found most satisfactory for the production of coronary sinus occlusion in the dog's heart. We believe that the method, with variations in technic in keeping with a somewhat different anatomic arrangement, may be applicable to the human heart and have therefore presented the procedure in this report.

AUTHOR.

White, James C.: Surgery of the Sympathetic Nervous System. J. A. M. A. **107**: 350, 1936.

Uniformly successful results have been obtained in all 18 cases of Raynaud's disease of the lower extremity by resecting the second and third sympathetic ganglions. Up to six years after operation results are as satisfactory as on the day of discharge. In the arm the operative results have, until recently, been far

less satisfactory. Six months after resection of the upper two thoracic ganglions (ten cases), or of these two and the inferior cervical ganglion (eleven cases), there was little improvement. The operation which proves to be the one of choice is that of cutting the sympathetic chain below its third thoracic ganglion and severing the communicant rami from the second and third intercostal nerves. This operation has now been performed twenty-eight times on eighteen patients, and observations over a period of one and a half years have demonstrated that the lasting increase in blood flow in the arm after this operation can be as great as in the leg.

Sympathectomy for other diseases than Raynaud's is discussed.

H. M.

Brown, W. S.: Successful Operation for Mesenteric Vascular Occlusion. Am. J. Surg. 32: 499, 1936.

A brief review of the literature is given. The rare cases of successful surgical intervention are described. In the author's case a large portion of gangrenous bowel, evidently ileum, was removed. The bowel was reunited. The microscopical report was acute hemorrhagic infarction with necrosis and acute purulent inflammation of the intestine. No cause for the occlusion was given.

H. M.

Bullrich, R. A.: Treatment of the Pain of Angina Pectoris With Cobra Venom. Rev. argent. de cardiol. 3: 111, 1936.

Because of the analgesic properties of cobra venom, it was used to relieve pain of patients suffering from angina pectoris. The results obtained in ten patients seem to be quite encouraging. In all cases pain was considerably decreased and the work-performing capacity was considerably increased; patients who could not walk more than 30 meters were able to walk a kilometer or more without trouble. This is a symptomatic treatment which has no appreciable effect on blood pressure or the electrocardiogram. The favorable effects disappear when the treatment is discontinued. To begin, the intravenous injections should be made every other day; once the condition of the patient has improved, the injection should be repeated every four to five days. No accident ascribable to cobra venom was recorded in any case.

AUTHOR.

Book Reviews

VASCULAR DISORDERS OF THE LIMBS. By Sir Thomas Lewis, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London; Honorary Physician to the Ministry of Pensions; Consulting Physician, City of London Hospital; Fellow of University College, London. New York, 1936, The Macmillan Company, Cloth, 8vo, 111 pages, $2.

This excellent volume has been written by an internationally recognized authority on many phases of circulation. Most of the material is from papers by the author and his associates previously published in the journal *Heart* and in the first two volumes of *Clinical Science*. The book, as the author states in the preface, is not a comprehensive account of vascular disorders of the limbs, and its value is somewhat lessened by the absence of controversial data and of a bibliography.

The author believes that "the time is opportune to attempt to outline conceptions of certain peripheral disorders of the circulation in a way that may prove useful to those engaged, not in research, but in practice." There is some doubt that the volume will serve this purpose since diagnosis and treatment are presented very incompletely and inadequately. The presentation is essentially that of a clinical physiologist interested in mechanisms rather than in diseases. The volume presents a definite contribution in this regard, as demonstrated in the chapters, "The Circulation in the Limb and Its Testing" and "Effects of Circulatory Arrest." In the chapter, "Embolism and Thrombosis of Main Arteries," however, the explanation of the marked diminution in circulation following arterial embolism is not altogether convincing. The effects of embolism on the circulation appear to be more profound than those of simple ligation or compression of an artery, and this needs further consideration. The short chapter, "Post-Ischemic Contracture: Intermittent Claudication," appears complete, but the thirteen-page chapter, "Arteriosclerosis; Thrombo-Angiitis Obliterans," is deficient in certain respects. The chapters, "Vasoconstriction: Local Arterial Spasm" and "Spasmodic Arterial Obstruction; Raynaud's Phenomenon," are clearly and concisely written. The explanation, however, of the uniformly good results which follow sympathectomy for Raynaud's disease of the lower extremities, in contrast to occasional failure of good results to follow sympathectomy for Raynaud's disease of the upper extremities, is not entirely convincing. Recent investigative work on this problem is not mentioned. The author believes that Raynaud's disease is a manifestation of local fault in digital arteries and that it is not attributable to overactivity of the sympathetic nervous system.

The chapter, "Gangrene (Bilateral Forms; Cervical Rib; General)," is well presented. The one, "Vasodilatation; Flushing," indicates that much remains to be done to clarify the subject. The term "erythrocyanosis" is used in place of the commonly used terms "cutis marmorata" or "livedo reticularis," but does not appear to be a better designation. The reader may be disposed to question the accuracy of the statement, "It came in with short skirts and thin stockings and will go out with them." The author raises objection to the term "erythromelalgia," and "erythralgia" is suggested as more appropriate. Since the term "erythromelalgia" is an accepted medical term, it would seem to the reviewer advisable to retain the latter.

No mention of the vasodilating syndrome frequently associated with polycythemia is made. Trial of sympathectomy is recommended for "erythralgia," but no reason is given for this recommendation, and no results are mentioned. This approach ap-

pears illogical to the reviewer since pain in this condition is aggravated by increasing the temperature of the skin, an anticipated result of successful sympathectomy. The final chapter, "Vascular Disorders in Diseases of the Nervous System," is clearly written and contains much valuable information.

This book constitutes an outstanding volume of explanations of the mechanisms of circulatory disturbances although it seems of limited value to the physician whose chief interests in peripheral vascular diseases are diagnosis and treatment. It is heartily recommended to every student of vascular diseases, since within its covers are to be found explanations of many of the puzzling phenomena observed in abnormalities of peripheral arterial circulation. It is the sort of work which can be read more than once with pleasure and referred to on numerous occasions with profit.

THE CLINICAL USE OF DIGITALIS. By Drew Luten, M.D., Springfield, Ill., 1936, Charles C. Thomas, 226 pages.

Those who are familiar with Dr. Luten's splendid work upon digitalis will be gratified to know that he has written a book upon its clinical use. They will welcome any work bearing his name with eagerness and confidence, nor will they be disappointed. He begins the preface of this volume with the following sentence: "Not many years ago there were published two classical works on digitalis, each a splendid epitome." Presumably he refers to the admirable work of Robinson and of Cushny, whose books appeared in 1923 and 1925, respectively. It is safe to say that future writers upon this subject must refer to three classical works, for the present volume more than measures up to the high standard of its predecessors.

As the title indicates, this is primarily a study of the clinical use of the drug, but all relevant experimental work has been included in the discussion of its action. It is essentially a summary of all the important work of the past ten years in this field, interpreted by one of the acknowledged authorities in the light of his own wide clinical experience. While most of his references are to work of the past decade, he has not hesitated to make use of important contributions during the preceding quarter century, and some of the most fascinating pages in the book are those devoted to the interpretation of cases reported by Withering and by Mackenzie. He states that he has made no attempt to harmonize conflicting opinion, but he has demonstrated convincingly that authoritative opinion is already in harmony upon almost all the essential points.

There are too many important chapters to permit comment upon all of them. There are few physicians, even among those who specialize in diseases of the heart, who cannot read the book with profit as well as with great pleasure. To those who have worked in this field, perhaps the most important chapters are those dealing with the effect of digitalis upon the ventricular muscle and with the newer views relating to the level of optimum effect and the doses required to produce it. The author brings forward evidence from many directions in support of the increasingly prevalent conception that the tachycardia commonly observed in cases of auricular fibrillation with heart failure is a result of the failure rather than a cause of it. "This conception explains the slowing from digitalis as due in large part at least to the beneficial effect which the drug is known to exert on the ventricular muscle regularly in cases of heart failure, and makes unnecessary the hypothesis that digitalis block depends solely upon a depression of conduction in the A-V tissues." To those unfamiliar with recent work upon digitalis, the amount of evidence supporting this view will be surprising. His comments upon the common practice of regarding auricular fibrillation in itself as an indication for administration of the drug are forceful and wise. He lends the weight of his authority to the current belief that digitalis increases the efficiency of a failing myocardium by enabling it to perform its work with a smaller expenditure of energy. He properly emphasizes the uselessness of the

drug in cases of toxic auricular fibrillation without heart failure and in cases of peripheral circulatory failure; he shows clearly that it should not be administered in cases of shock, septicemia, pneumonia, and other acute infections. The sections relating to the therapeutic zone of digitalis action and the differences in dosage required for different levels of optimum effect are extremely important.

The longest chapter in the book is that upon dosage and method of administration; to these important matters the author devotes sixty-four pages, every one of which is important. If every practitioner could be required to read this one chapter thoughtfully and repeatedly, the improvement in the therapeutic use of digitalis would be enormous. There is no aspect of its therapeutic or toxic action that is not fully and wisely discussed.

The book closes with a quotation from Wenckebach: "Digitalis treatment is one of the most important and serious duties of the general physician; it demands a great deal of skill, power of observation, keen interest, and experience. A long life is too short to learn enough about this wonderful drug." To the writing of this book, Dr. Luten has brought in abundant measure the requisites mentioned by Wenckebach. There is not a page that does not bear witness to his wide experience, his excellent clinical judgment, and his deep interest; there are scores of paragraphs that could have been written only by a wise, kind, experienced physician whose first concern is for the welfare and comfort of his patients. His book takes its proper place on the shelf with those of Cushny and Robinson as the latest in a series of splendid critical reviews. Because it is the latest, because it includes so much work that is new and of fundamental importance, and especially because of the author's distinction, wisdom, and clarity of expression, it stands, in the opinion of this reviewer, as the finest work upon digitalis available today.

Books Received

KLINIK UND THERAPIE DER HERZ-KRANKHEITEN UND DER GEFASSER-KRANKHEITEN. Vorträge für Praktische Ärzte. Von Privatdozent Dr. D. Scherf. Dritte verbesserte und Vermehrte Auflage. Pp. 290. Mit 10 Textabbildungen. Wien: Verlag von Julius Springer, 1936.

OVER VENTRICULAIRE EXTRASYSTOLEN EN HARE LOCALISATIE. PROEFSCHRIFT. Ter verkrigging van den graad van Doctor in de Geneeskunde aan de Hoogeschool te Batavia, op Gezag van den Voorzitter der Faculteit, Dr. B. J. van der Platts, Hoogleeraar in de Faculteit der Geneeskunde, tegen de Bedenkingen van die Faculteit te Verdedigen op Vrijdag 29 Mei 1936, des Voormiddags 12 Uur. By Cornelis Johannes Storm. Pp. 193. Paper. G. Kolff and Company. Batavia-C. 1936.

ELECTROCARDIOGRAFÍA PRÁCTICA. By Luis Hervé L. Ayudante de la Catedra de Patologia Médica de la Universidad de Chili. Pp. 69. Paper. Libreria e Imprenta "Artes y Letras"; Santiago de Chili; 1936.

ROENTGENKIMOGRAFÍA CONCÉNTRICA. By Alberto C. Morelli. Instituto de Radiologia; Profesor Carlos Butler. Pp. 34; 32 plates. Montevideo. 1936.

CARDIOPATIAS CONGENITAS. By Ramon Valdivieso D., Profesor Agregado de Terapéutica, and Domingo Urrutia M. Ayudante de Clinica Médica. Prologo del Prof. E. Gonzalez Cortes. Pp. 158; 48 illustrations. Paper. Santiago de Chili; 1936.

INDEX TO VOLUME 12

An asterisk (*) after a page number indicates that the reference is an abstract and not an original article.

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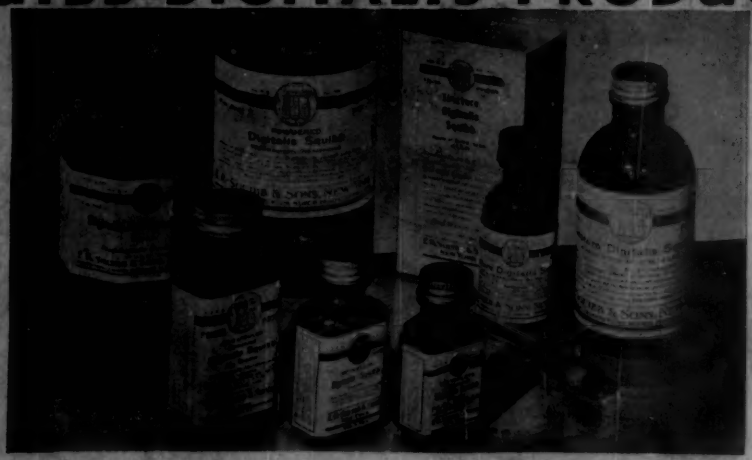

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